*Journal of the*

# AMERICAN PHARMACEUTICAL ASSOCIATION

VOL. VIII, NO. 11 NOVEMBER, 1947 CONSECUTIVE NO. 21

*Practical Pharmacy Edition*

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**FRONT COVER: The consistent and sharp upward trend in the growth of the American Pharmaceutical Association is indicated by the illustration. In a decade the total membership has climbed from 3400 to 15,707. Prior to 1943 Association statistics did not segregate active and associate members, as reflected in the chart. At present about two-thirds of the membership is comprised of active members and one-third of associate (student) members. Of the A. Ph. A. active members at least two-thirds are practicing pharmacists. For information on geographic distribution see page 480.**

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WHAT IS ACCURACY?

THERE should be no complacency about the data on prescription tolerances presented on page 541. For any pharmacist interested in his profession, the time required to digest this material will be well invested.

Progress in developing and applying standards of accuracy with specific reference to prescription technique has lagged behind the development of official drug standards and their application in manufacturing laboratories. As Goldstein implies, and will bring out more clearly in subsequent articles, the two are not necessarily synonymous. The prescription balance and conical graduate will never replace the analytical balance and volumetric apparatus as instruments of accuracy. Nor is the precision of the latter necessary to provide the pharmacist with a just claim to "prescriptions accurately compounded."

What *is* proper "accuracy" in prescription practice? It has not been shown whether this can be answered satisfactorily in a quantitative way. In Goldstein's opinion present official drug standards and a rule-of-thumb $\pm 10\%$ are not necessarily the final criteria of prescription accuracy.

Until there is a more widely accepted yardstick of prescription tolerances, there will probably continue to be charges and countercharges concerning the number of pharmacists who are not measuring up to the traditional basic concept of the profession: prescription accuracy.

Recent reports on analytic checks of prescription service in several states are fundamentally disturbing. There are apparently either (1) too many variables in compounding to measure the advantages of individualized prescription service against the tolerances used in these studies, or (2) too many pharmacists occasionally or habitually fail to control adequately those factors that determine accuracy: interpretation of the prescription, arithmetic calculations, equipment, ingredients, technique and care in compounding.

Whatever the situation may be, members and delegates at the 1947 A. PH. A. convention felt that there should be further exploration of the question: What are reasonable prescription tolerances? They passed a resolution asking the Council to consider the need and necessary procedure for a comprehensive study.

The A. PH. A. Committee on Prescription Tolerances and others already have done a great deal of spade work in this field. The Council will need to determine whether there should be built upon this foundation a broad-gauge, positive program that will give further guidance to the pharmacist, and law enforcement official.

This would appear to be most productive if a controlled study were made—under some authoritative agency such as the A. PH. A. laboratory—to show what tolerances are practical for various types of prescriptions when compounded under ordinary conditions of practice, using equipment of a known degree of accuracy.

It also seemed clear from the discussion of prescription tolerances at the A. PH. A. convention that we have a need for more specific information on variations in accuracy introduced by variations in prescription technique. Without this frame of reference it would be even more difficult to give any definite expression to "reasonable prescription tolerances."

To make such a study meaningful there must also be emphasis on adequate equipment. The literature repeatedly emphasizes inaccurate equipment as a frequent cause of inaccuracy, a factor which the greatest competence never nullifies. There should be an impartial study of the accuracy of available equipment and guidance on the calibration of apparatus and periodic checking of weights and balances.

However, prescription accuracy is also largely a result of the pharmacist's mental attitude. To establish the proper state of mind is a responsibility of our educators and the apprentice's preceptor. To cultivate it, should be a function of pharmacy's organizations and journals.

If a broad program to clarify the problem of prescription tolerances evolves, it will lack meaning in some areas unless there are additional facilities set up at the level of the state government or state association. We have in mind support of an informational program for pharmacists, aid to pharmacists in checking equipment, and a periodic analysis of prescriptions dispensed.

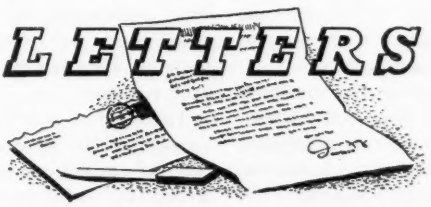
Whenever "reasonable" prescription tolerances are applied, the conscientious pharmacist need have no misgivings about an analytic check on his service. As James Hill of Niagara Falls put it at the A. PH. A. convention, such a check by the state amounts to free analytic control, a service on which the drug manufacturer spends thousands of dollars to check mass-produced products.

## A MEMBER CALLS FOR UNITED SUPPORT

Sirs:

This letter could well be directed to every practicing pharmacist who isn't a member of his state association or the AMERICAN PHARMACEUTICAL ASSOCIATION. . . . These men are willing to go along day in and out and leave to luck the improvement of conditions in pharmacy. The profession has taken terrific strides in the past twenty years toward putting pharmacy in a new suit: a "coat" of *prestige* and "trousers" of *respect* in the eyes of the entire nation!

The various association officers, representing pharmacy, fight tenaciously to better conditions while many of the non-members are "in the arms of Morpheus." These non-members are profiting indirectly through the untiring efforts of these few.




Common sense teaches us that "united we stand and divided we fall." This adage applies to the many pharmacists that remain unsigned by their state association and flee from its ranks as though it were a plague! There is nothing to fear, but much to gain. The more that join, the better the future of pharmacy, which is definitely on the upward climb.

Every state association in the country should include with its state member application, blanks with which to join the A. PH. A. There is no reason in the world why all pharmacists shouldn't become members of the nation's mouthpiece of pharmacy, the A. PH. A. It would certainly be foolish to assume that one could build a house without a foundation! The A. PH. A. is that foundation, and the state associations are the houses we build to live in.

The advantages offered by the A. PH. A. to the profession are unlimited. The larger the army of members, the easier the task becomes toward improving conditions in general. The two monthly editions of the JOURNAL, the *Scientific Edition* and the *Practical Pharmacy Edition*, are literally a University of Knowledge and worth many times the price for annual membership. It keeps one abreast with scientific progress, thus enabling us to perform better our duties as pharmacists. It keeps us posted on current legislation affecting our profession.

A glance at the daily itinerary of our present secretary, Dr. Robert P. Fischelis, will give you an idea of what a herculean job he holds. His work is incessant and hard. "For what purpose?" you ask. For your benefit and mine; for the good of the profession. But he must have members to back him up. Let all pharmacists that aren't affiliated with the A. PH. A. resolve today to join! Remember, we do get so *much* for so *little*. Our standards are getting higher and will reach perfection only with a strong professional organization.

Be proud of the fact that you are a pharmacist and one of the nation's "watchdogs of health." Be justly proud that you are a member of the A. PH. A. and doing your share towards upholding the principles for which it stands and fights.

Asbury Park, N. J. — FIORE JOS. VENERI

## COMPLIMENTS FROM CANADA

Sirs:

The only criticism of the JOURNAL to date has been that we do not have sufficient copies to meet the demand of the students.

Is it possible for a college such as this in Canada to procure copies in addition to that of the individual membership subscription? The copies of the JOURNAL are in daily use by members of our professional classes. This applies not only to the current issues but to copies in our files dating back several years in which the students are able to follow the development of thought on such subjects as washable ointment bases and like topics of importance.

Halifax, Can. — JESSIE I. MACKNIGHT

*Assorted compliments from various Canadian colleagues have been appreciated. Extra subscriptions of the* PRACTICAL PHARMACY EDITION *to mailing addresses in Canada are now $4.35 a year.*—THE EDITOR

## MUSIC HATH CHARMS

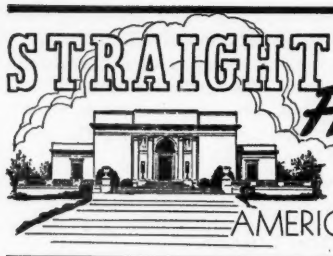
Sirs:

I am a member of the A. PH. A. student branch at Columbia University College of Pharmacy and I enjoy reading the *Practical Pharmacy Edition* very much. Being a music lover and an amateur humorist, I jotted down the following as my impression of the type of prescription we may have to fill in future years if further advances in the therapeutic use of music are made as indicated in the item on this subject in your September issue, page 462. Please note that the prescription is a narcotic:

| | | |
|---|---|---|
| Tincture of "Sugar Plum Fairies" (Tchaikovsky) | 10. | cc. |
| "The Red Poppy" (Oliere) | 0.1 | Gm. |
| "Love of Three Oranges" (Prokofieff) | 3.0 | |
| "Gold and Silver Waltz" (Lehar) | 5 | bars |
| "The Sea" (Debussy) | *q.s.* | to make one therapeutically effective concerto. |

Sig: Play one album three times a day after meals.

New York City — MARVIN L. SILVER



# STRAIGHT FROM HEADQUARTERS

by ROBERT P. FISCHELIS, Secretary
AMERICAN PHARMACEUTICAL ASSOCIATION

## *DRUG DISTRIBUTION THROUGH PROFESSIONAL CHANNELS*

WITH one conspicuous exception there has been unusual unanimity of opinion and action within the drug industry on matters of common interest during the past year.

The conspicuous exception is the continued aggressive opposition of the Proprietary Association to efforts to safeguard the distribution of drugs by limiting such distribution to pharmacies.

The Proprietary Association is a member of the National Drug Trade Conference. It is to be presumed that all members of that Conference are interested in the public health. It is presumed that they know that the governments of the various states have created a class of licensees to deal in drugs, medicines and poisons and to compound prescriptions. This class of individuals has been created because the public knows that drugs and medicines are not mere merchandise to be distributed in the same manner as candy, groceries and dry goods.

It continues to be a source of great surprise to all others engaged in the practice of pharmacy that this one group goes to great lengths on the one hand to impress the public with the scientific nature of its products and on the other hand encourages and even urges the distribution of such products through non-professional outlets.

It is always unfortunate when the internal problems of any profession or industry are aired in public, because the general public does not understand the details of such controversies. Under such circumstances members of state legislatures (which, under the police powers granted the states, regulate the practice of pharmacy) may obtain the impression that there is a division in the profession of pharmacy. This is not the case. However, when members of the profession appear before committees of the legislature to request restrictive legislation in the interest of the public health, these committees are visited at the same time by representatives of the Proprietary Association. The latter also make claims about being interested in the public health but plead for legislation giving the privileges of drug distribution to wagon peddlers, general storekeepers and other non-professional retail outlets. The members of the legislature are naturally confused.

This kind of activity is properly resented by members of the profession of pharmacy and, as a result of a recent incident in the state of Georgia, a resolution was presented to the AMERICAN PHARMACEUTICAL ASSOCIATION at its Milwaukee convention last August which read as follows:

> "WHEREAS the various state pharmaceutical associations, in their attempt to strengthen and perfect laws regulating the control and sale of dangerous drugs, have found to their dismay that representatives of the Proprietary Association have taken steps to prevent passage of these laws, or to weaken them by amendments, be it therefore
>
> "*Resolved* that the A. PH. A. condemn such practice on the part of the Proprietary Association, and respectfully urge that in the future the Proprietary Association register its protest, if any, with the constituted officials of the state boards or associations."

The Committee on Resolutions expressed sympathy with the purpose of this resolution and recommended that it be transmitted to the Council for action. The House of Delegates and the ASSOCIATION concurred in the recommendation of the Committee.

The members of the Georgia State Pharmaceutical Association who were active in the presentation of this resolution include a past president of the AMERICAN PHARMACEUTICAL ASSOCIATION and the dean of a college of pharmacy. Certainly these men command respect and are not apt to consider it necessary to introduce a resolution of this kind if they had not met with an unusual form of opposition to the presentation of legislation which they considered in the interest of public health.

However, the A. PH. A. Committee on Resolutions which considered this matter reported to the House of Delegates that it was in sympathy with the purpose of the resolution but recommended that it be transmitted to the Council of the AMERICAN PHARMACEUTICAL ASSOCIATION for action. Before the Council could act on the matter, the Proprietary Association issued a public statement based upon a report that the resolution submitted by the Georgia Pharmaceutical Association had been adopted.

The Proprietary Association, like several other national pharmaceutical associations, is represented in the House of Delegates by an accredited delegate. This delegate had every opportunity to learn of the disposition of the resolution in question and he could have spoken in opposition to the resolution, had he desired to do so. The floor of the House of Delegates is open to any delegate and, furthermore, members of the AMERICAN PHARMACEUTICAL ASSOCIATION who are not accredited delegates may also speak in the House of Delegates, although they have no vote in the House.

Therefore, there was every opportunity for this matter to be thoroughly discussed in the House of Delegates. No such discussion took place, because the representative of the Proprietary Association did not choose to speak on the subject.

The point we wish to make is that there is a forum in American pharmacy for the discussion of these matters and it should be taken advantage of by those who are sincere in their efforts to promote the public health and welfare and the profession of pharmacy.

In place of discussing the matter within the profession the Proprietary Association chose to issue a public statement on September 10, in which it pointed out that it has never interfered with and has in fact assisted in the passage of laws regulating traffic in dangerous drugs and narcotics.

The statement went on to say that the Proprietary Association's representatives have always been willing to cooperate with state boards and associations in the drafting of legislation pertaining to the regulation of the practice of pharmacy.

This was followed by a complaint that state boards or associations rarely, if ever, contact drug industry representatives prior to the introduction of legislation amending the pharmacy laws.

The statement continued as follows:

"If and when the state boards or associations honestly desire to bring up to date the laws regulating the practice of pharmacy, the cooperation and assistance of the Proprietary Association will be forthcoming. However, if such proposals cover the field of merchandising and attempts are made to restrict the sale of proprietary products which meet with the requirements of the Federal Food and Drug Act and which are offered for sale to the general public, there must of necessity be a parting of the ways. There can be no retrogression in the proprietary articles industry, only progression in pace with the art and science of medicine."

It will be noted that in this statement the honesty of state boards and associations in bringing laws regulating the practice of pharmacy up to date is questioned. It would be of interest to the profession of pharmacy to learn from the Proprietary Association how the promiscuous sale of drugs and medicines through unregulated channels can be considered a part of the progress in the art and science of medicine.

We believe that Mr. Leslie D. Harrop, attorney for the American Drug Manufacturers' Association, gave the answer to all of this in his splendid address before the AMERICAN PHARMACEUTICAL ASSOCIATION at the Milwaukee convention. Mr. Harrop pointed out that the kind of activity to which the Georgia State Pharmaceutical Association, among others, objected is the effort to build up a general exemption from exclusive distribution in the drugstore of an ever-increasing number of drug products. "Carried to its quite logical conclusion," said Mr. Harrop, "the effects of these activities, if successful, will within a short time leave the pharmacist with the dubious distinction of being able to say he is the only person who can fill prescriptions. And he will also realize that without a day of training in pharmacy John Jones who had the minimum amount of common schooling can sell in the corner grocery store about 95% of the medicines used by the public."

Mr. Harrop also points out that in support of this type of activity, advantage is being taken of the Federal Food, Drug and Cosmetic Act by claiming that this act was passed to extend or promote self-medication. The entire legislative record in connection with this Act shows that it was aimed at making self-medication, when undertaken, a safer method of treating disease by giving to the layman who chooses to be his own doctor, better information concerning the properties of the drug he proposes to use.

From such intent, however, the interpretations have veered sharply. Instead of a law to assure

(*Continued, page 582*)

# A NEW MORPHINE-LIKE ANALGESIC

by NATHAN B. EDDY

SECRETARY, COMMITTEE ON DRUG ADDICTION AND NARCOTICS, NATIONAL RESEARCH COUNCIL

**POWERFUL SYNTHETIC DRUG—VARIOUSLY KNOWN AS AMIDONE, METHADON, DOLOPHINE, ADANON, 10820 AND AN-148—IS NOW AVAILABLE AS USEFUL SUBSTITUTE FOR MORPHINE IN MOST TYPES OF PAIN . . . LESS SEDATION AND LITTLE RESPIRATORY OR CIRCULATORY EFFECTS OBSERVED IN CLINICAL TRIALS; ADDICTION LIABILITY PLACES IT UNDER NARCOTIC CONTROL**

AT THE close of the war in Europe the Foreign Economic Administration of the State Department organized teams to investigate German chemical industry. The report of one of these* included information on progress the Germans were making in the field of analgesics.

In the 1930's the Germans were looking for an antispasmodic as a substitute for atropine and developed a compound which they called Dolantin. Quite incidentally they discovered that this was a better analgesic than antispasmodic and they introduced it to medicine as such in 1939. Subsequently Dolantin (known in this country as Demerol) was shown to possess many morphine-like properties including those of tolerance and addiction liability, but its analgesic potency was more nearly like codeine than morphine.

The Germans made many Demerol derivatives, but apparently none showed more than minor improvement. At the same time they were developing a series of diphenyl derivatives and some of these showed remarkable activity. The outstanding example of the series, as outlined in the Kleiderer report, the Germans called "10820" or "Amidon." Accounts of this substance have appeared in American literature under these designations and as "Dolophine" and "AN-148." Methadon is the name recommended for it by the Council on Pharmacy and Chemistry of the American Medical Association. Amidone is the name which will be used in this report because it has been most commonly employed in the investigative work to which reference will be made.

It should be emphasized, however, that all of the names mentioned refer to the same chemical entity. Amidone then is 6-dimethylamino-4,4-diphenyl-3-heptanone.† Chemically it is not at all related to morphine nor directly to Demerol. It is somewhat related to a diphenyl ethanolamine which has been described as mildly analgesic, but which is not at all morphine-like. (The structural formulas for these compounds are shown on the facing page.)

The hydrochloride of Amidone is a white crystalline substance, soluble in water to about 5%, of bitter taste, and somewhat irritating when injected subcutaneously. Amidone is a racemate and has been resolved into its levo- and dextrorotatory isomers.

The racemate and the isomers have about the same toxicity in laboratory animals, but the analgesic effect and other morphine-like properties are exhibited chiefly by the *l*-form. In animals Amidone is three to ten times more toxic than morphine, according to the species, and two to three times more toxic than Demerol, but its analgesic effect is twice that of morphine and 10 times greater than that of Demerol so that it still has a very wide margin of safety.

Amidone has been administered to all of the common laboratory animals (both intact and in some instances animals with various parts of the nervous system destroyed) and to man (normal individuals, patients needing sedation or relief of pain, and known morphine addicts). In almost every instance and condition the effect of Amidone is qualitatively the same as that of morphine.[2–11] It produces such typical morphine effects as the Straub reaction in mice (which has been used as a biological test for the

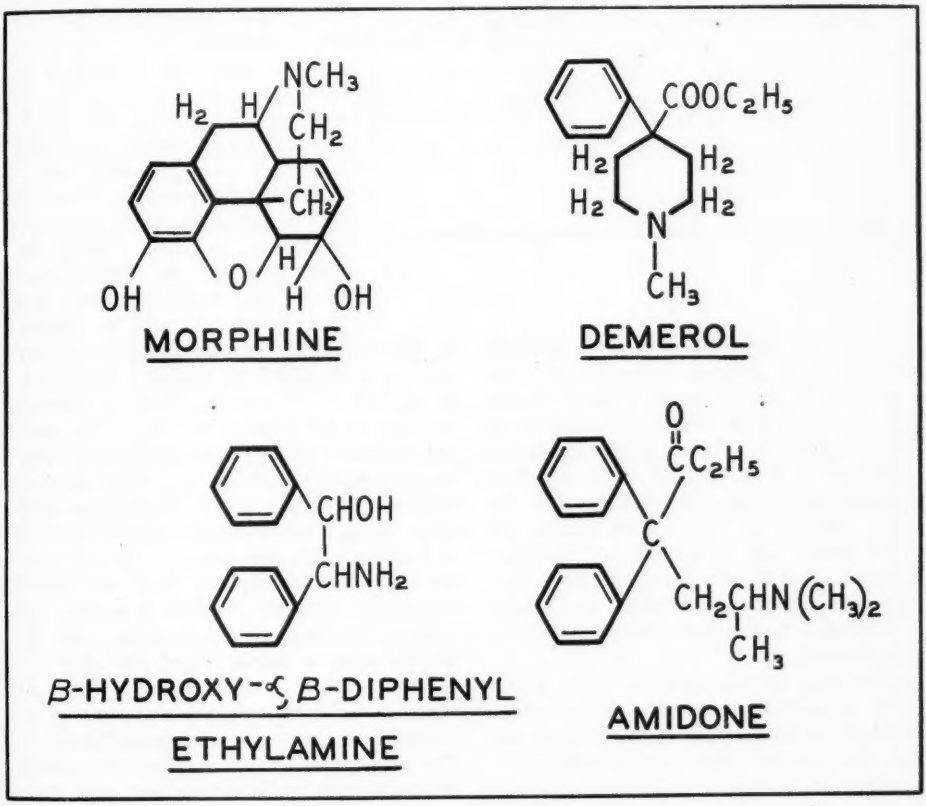
* The team for medicinal and pharmaceutical chemistry was headed by Dr. Kleiderer of the Eli Lilly organization. Its report was prepared for publication by the Department of Commerce in the Fall of 1945.[1]

† Some reports have erroneously given the chemical name of Amidone as 1,1-diphenyl-1-(dimethylaminoisopropyl)-butanone-2, on account of an initial misunderstanding.

presence of morphine), purposeless excitement in cats and euphoria (with large doses) in man. Its effect on behavior and reflex activity in decorticate, decerebrate and spinal dogs and cats duplicates that of morphine. It has an effect similar to that of morphine on circulation and respiration and on smooth muscle, at least of the intestine. Tolerance to Amidone can be developed in animals (except perhaps the monkey) and in man as with morphine though somewhat

tory depression or significant circulatory change.

The principal side effects have been dizziness, nausea and vomiting. These untoward reactions seem to vary more with the activity of the patient than with the mode of administration. For example, in a group of cancer patients, who were mostly bedridden, to whom Amidone was given parenterally for pain relief, side reactions appeared in less than 5%. On the other hand, in a group of normal individuals who were com-




more slowly. The drug has definite addiction liability.

Thousands of doses of Amidone have now been given to patients in this country with all types of clinical conditions.[12–16] Administration has been oral and parenteral (subcutaneous, intramuscular and intravenous) and the indications for its use have been as varied as for morphine. This clinical experience has shown that Amidone is an effective analgesic for man; as a rule, the dose required for adequate pain relief is about two-thirds the dose of morphine under the same conditions. Single analgesic doses produce less sedation than morphine and usually no respira-

pelled to be ambulatory during observation, to whom Amidone was also given parenterally, nausea and vomiting occurred in almost 50%. After oral doses of Amidone, where the patients were usually ambulatory, side reactions have been reported in 25 to 50% of trials. This relation of side effects to ambulation is usually a disadvantage; it can be an advantage in certain cases where bed-rest is desirable, compelling such rest to avoid the undesirable effects. The relatively slight sedative effect of analgesic doses also can be an advantage or disadvantage—a disadvantage particularly in pre-anesthetic medication and in other cases where anxiety is a symp-

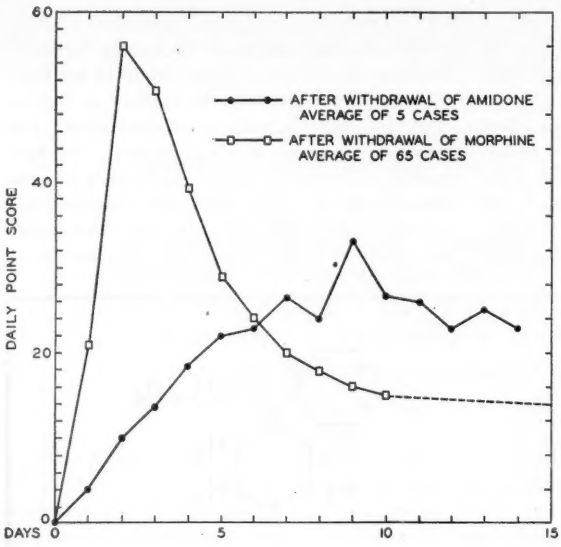



**FIGURE 1—Intensity of abstinence symptoms after administration of Amidone for four and one-half to six months. In Figs. 1 and 2 abstinence intensity is plotted according to the method of Kolb and Himmelsbach.[22]**

tom that the physician desires to alleviate.

Though single analgesic doses produce little or no effect on respiration the principal danger of overdosage will be respiratory failure as in morphine poisoning. Less profound depression (coma) may follow Amidone overdosage than with morphine but the treatment should be the same; namely, directed toward keeping the patient awake and application of respiratory stimulants or artificial respiration. As in morphine poisoning one should also watch closely the circulation because both drugs act similarly in this respect.

Experiments to determine the effect of prolonged administration of Amidone have been carried out on mice and rats, dogs, monkeys and man. In addition there is accumulating information on prolonged administration under clinical conditions. Mice and rats develop tolerance to the analgesic effect of Amidone about as with morphine both in speed and degree. Dogs, intact, decorticate, decerebrate and spinal animals, develop tolerance to various effects of Amidone as rapidly as with morphine if multiple doses per day are given. In addition, all of these dogs develop dependence upon Amidone (addiction) more rapidly and more intensely than with morphine, so that when the drug is stopped after a month or more of administration a definite and intense abstinence picture appears within a few hours.[17] According to Woods, Wyngaarden and Seevers,[18] monkeys, given small doses of Amidone subcutaneously once daily, developed neither tolerance nor dependence.

Isbell and his co-workers[19,20] have administered Amidone to former morphine addicts, who volunteered for the experiment. The drug was given four times daily subcutaneously for periods up to six months and in increasing amount up to 100 to 200 mg. per dose. During the first day or two the sedative effect of the drug increases slightly and then tolerance begins to appear so that the individuals are almost completely tolerant to the effects of the large doses given at the end of six months. They are tolerant not only to the sedative but also to the analgesic and other effects of Amidone, but the tolerance development is slower than with morphine under similar circumstances. These former morphine addicts show a distinct euphoric reaction to Amidone which they describe as entirely comparable to that of morphine, heroin and related substances. The dose required to produce this euphoric reaction, however, is larger than the minimal analgesic dose of clinical practice.

When Amidone is stopped abruptly after six months' administration to the post-addict group a definite abstinence picture appears (*see fig. 1*). This develops more slowly and is less intense than after morphine but is definite and quite characteristic. It can only be interpreted as indicative of physical dependence in these individuals as with morphine.

In clinical practice Amidone has been administered for relief of pain in many individuals, who have not previously received much morphine, for periods of one to six months. Among these cases there has been so far little evidence of tolerance to the analgesic effect of the drug and signs of physical dependence (addiction) have been observed only once.[21]

Turning again to the administration of Amidone in relation to morphine addiction, it has been demonstrated[20] that it will substitute for morphine smoothly and completely in a known

addiction, preventing entirely the abstinence phenomena which would otherwise develop when morphine is withdrawn. Later, after days or weeks of Amidone substitution, the drug can be stopped abruptly and there will develop a less intense abstinence picture than is usually seen on abrupt withdrawal of morphine (*see fig. 2*). This may mean a useful role for Amidone in the treatment of morphine addiction, permitting a smooth substitution for morphine and a less stormy withdrawal period than by any of the methods of treatment now in use.

To sum up, Amidone is a powerful analgesic for most types of pain which also exhibits most of the other effects of morphine. In ambulatory patients its use will be attended by unpleasant side reactions—dizziness, nausea and vomiting—about as often as with morphine. Overdosage will cause respiratory depression and prolonged administration probably constipation. Tolerance to it can be developed as with morphine. A euphoric reaction may be observed, especially if doses larger than necessary to control pain are given. It must be considered to have definite addiction liability. Finally, because of its morphine-like characteristics it is practically certain that so far as it is available Amidone will be abused by those individuals who seek relief in drugs for their inadequate adjustment. This abuse will certainly lead to habituation and probably to physical dependence. It is vital, therefore, to apply the same control and restrictions in respect to both manufacture and handling of Amidone as are applied to morphine. And

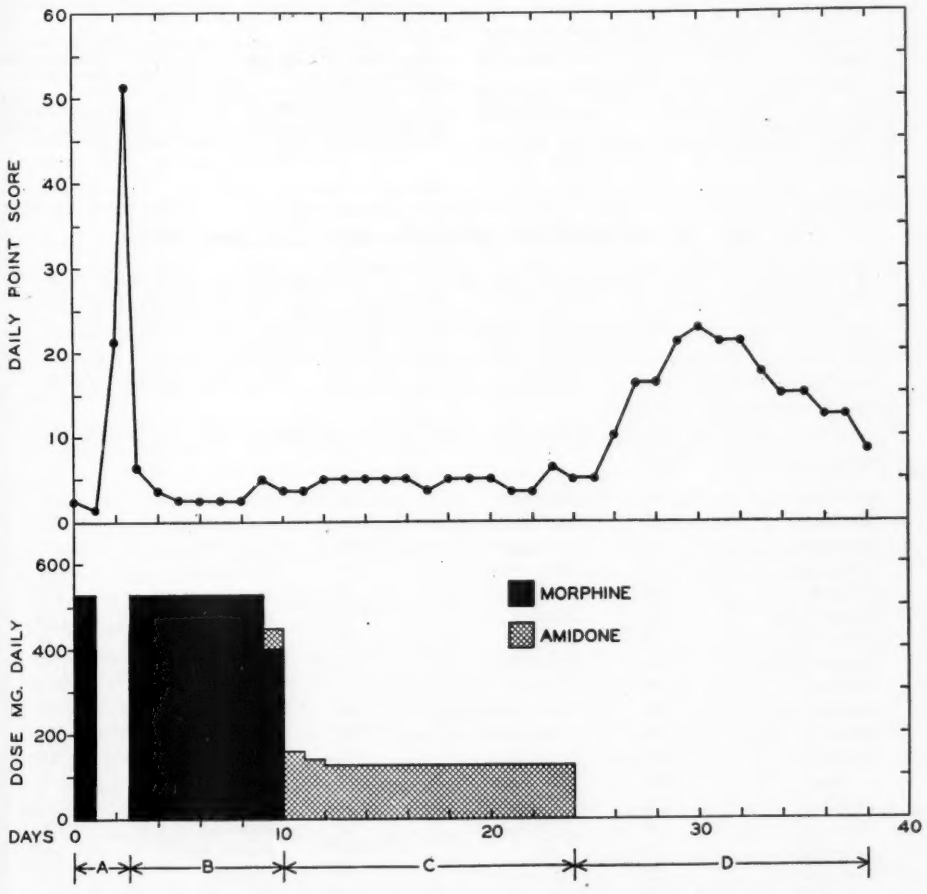



**FIGURE 2—Abstinence picture upon substitution of Amidone for morphine. Average of 12 cases. (A) Preliminary withdrawal of morphine; (B) Restabilization on morphine; (C) Substitution of Amidone; (D) Withdrawal of Amidone.**

the physician should employ the same precautions in its use as he would with morphine and related substances.

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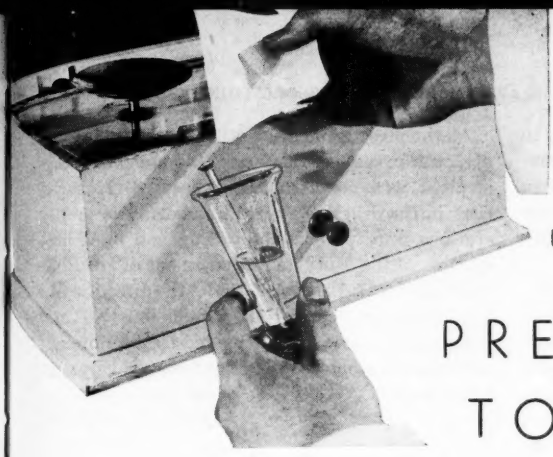
## A. PH. A. MEMBERSHIP REACHES NEW ALL-TIME HIGH

THE front cover of this issue portrays graphically the continued upward trend in the membership of the AMERICAN PHARMACEUTICAL ASSOCIATION as the 1946–47 ASSOCIATION year came to a close. At the time of the Milwaukee convention there were 15,707 members, consisting of 10,264 active members, 5426 associate (student) members and 17 honorary members. Among the active members are 342 life members. A decade ago the total A. PH. A. membership was 3400.

At the end of the 1946–47 ASSOCIATION year the active membership was distributed geographically as follows:

| | | | | | |
|---|---|---|---|---|---|
| Alabama | 93 | Maryland | 226 | Rhode Island | 34 |
| Arizona | 28 | Massachusetts | 385 | S. Carolina | 61 |
| Arkansas | 44 | Michigan | 549 | S. Dakota | 63 |
| California | 715 | Minnesota | 178 | Tennessee | 94 |
| Colorado | 106 | Mississippi | 109 | Texas | 163 |
| Connecticut | 130 | Missouri | 194 | Utah | 33 |
| Delaware | 13 | Montana | 39 | Vermont | 7 |
| Distr. of Colum. | 124 | Nebraska | 102 | Virginia | 160 |
| Florida | 99 | Nevada | 5 | Washington | 125 |
| Georgia | 122 | New Hampshire | 65 | W. Virginia | 68 |
| Idaho | 18 | New Jersey | 755 | Wisconsin | 586 |
| Illinois | 578 | New Mexico | 49 | Wyoming | 12 |
| Indiana | 265 | New York | 1090 | Alaska | 3 |
| Iowa | 123 | N. Carolina | 107 | Canal Zone | 9 |
| Kansas | 91 | N. Dakota | 29 | Hawaii | 20 |
| Kentucky | 76 | Ohio | 695 | Puerto Rico | 108 |
| Louisiana | 125 | Oklahoma | 48 | Canada | 86 |
| Maine | 59 | Oregon | 170 | Other Foreign | 174 |
| | | Pennsylvania | 854 | | |



FACTORS AFFECTING ACCURACY IN COMPOUNDING, THE FIRST IN A SERIES ON Rx STANDARDS

by SAMUEL W. GOLDSTEIN*

# PRESCRIPTION TOLERANCES

EARLIER attempts to determine the kind and extent of errors in prescription compounding have been published, but no satisfactory explanation or corrective recommendations have been offered.

Andrews[1–5] published a series of articles dealing with this subject. All the compounding and at least some of the checking of the prescriptions used in his study were the work of undergraduate pharmacy students. This nullifies to a large extent what might have been a major contribution toward clarifying this problem.

A bulletin[6] on prescription tolerances published by the ASSOCIATION in 1933 criticized the actions of some drug control officials as presenting to the public an incorrect picture of pharmaceutical activity. It pointed out that slight variations in quantities of prescription ingredients are due to various factors, many of them beyond the control of the compounder, and when these factors are not given proper consideration by law-enforcement bodies injustices may follow. A committee had been appointed in 1932 to make a study of what constitutes reasonable deviations in prescription ingredients and to establish reasonable tolerances. The first results of the efforts of this committee dealt with powders and capsules and were published in 1934.[7]

The Committee studied 600 prescriptions for powders containing two parts of charcoal and one part of heavy magnesium oxide. They eliminated all the preparations whose total weight varied by more than 10% from the prescribed total weight. Over 90% of the 125 discarded products had been prepared by students or Board candidates. This emphasizes the fallacy in using students in surveys of this type. The percentage of the remaining 450 prescriptions that were compounded by students is not mentioned. Weights of the individual powders in each set of ten gave the following results: About 18% of the preparations failed to fall within a ±20% variation; and about 51% failed to fall within a ±10% variation. Then, apparently, they based their conclusions on the fact that a group of students, who were told their work would be checked, put up powders reported within a ±10% variation.

One of the four factors to which the Committee attributed the great variation in total weight in the discarded preparations was faulty weights or balances. When it is noted that over 90% of these prescriptions were filled by students and Board candidates, inclusion of this factor is a direct indictment of the condition of the weights and balances in the college of pharmacy where the work was done. Which school participated I do not know. If such a condition exists in the schools, how can we expect to turn out pharmacists who properly recognize the importance of correct weights and balances?

A survey conducted by L. M. Kantner in 1941 in the drugstores of Maryland revealed that many faulty balances and incorrect weights were being used. About fifty prescription balances and at least a thousand weights were condemned.

For the past several years the reports of the A. PH. A. Committee on Prescription Tolerances have dealt mainly with the problem of improving the equipment used in filling prescriptions. The 1944 report of the Committee states that the real answer to this part of the problem is a minimum equipment law such as was first passed in Maryland.

The "eye" method of dividing powders, which the Committee reported as satisfactory, introduces the personal factor. Everyone does not have the same ability to judge amounts of powders visually. The same individual will not judge in exactly the same manner at all times. Physi-

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The author thanks W. F. Reindollar, chief of the Bureau of Chemistry, for the use of his Annual Reports and the Bureau files.

cal well-being in general and optical condition in particular will play a part. Whether the prescription is filled in the late part of the day when fatigue sets in is important. Certainly, whether the prescription is filled leisurely or hurriedly will affect the accuracy of divisions.

The non-toxic nature of ingredients in powders such as the one used in the Committee's study might also tend to cause laxness on the part of the pharmacist. It should follow that with more toxic ingredients greater precision could be expected.

The Committee's 1934 report also gave the results of a study of prescriptions for 5-grain and 3-grain capsules of the same mixture used in the powders. In the first group the gross weights varied from 5.6% to 15.8% below the theoretical weight, with variations from +12.4% to −37% in the individual capsule contents. In the 3-grain sets the gross weights showed variations of −7.3% to −22.7% from the theoretical, and individual capsule content variations of +7.7% to −37%. Neither the compounders nor the manner in which the preparations were checked were described.

**The Committee found that variations among empty capsules No. 0, 1, and 4 were ±11.9%, ±9.2%, and ±8.1%, respectively. Since most pharmacists use an empty capsule as a tare when they do weigh a filled capsule, it is obvious that a large error is introduced in this manner.**

A further program of study was outlined in the 1934 Committee report but no later reports were made on the suggested studies. It is possible that the data obtained in the preliminary study of capsule-filling accuracy frightened them away from further investigation. Public health workers have recently made surveys of compounding accuracy under actual drugstore conditions and have published their findings.[8, 9] Their revelations in no way give aid to those who insist that prescription compounding should be considered an exact science. The present study is an attempt to clarify the problem of compounding inaccuracies and to determine what corrective steps can be recommended.

All the prescriptions and other extemporaneous preparations used in this study, and not otherwise credited, were compounded by licensed pharmacists in the drugstores of Maryland. The preparations were purchased by drug and food inspectors of the Maryland Department of Health, especially by H. Bernhardt, under the direction of L. M. Kantner, deputy drug commissioner. The samples were sealed and delivered to the Bureau of Chemistry where they were tested and analyzed by the author.

## Capsules

We have tested five prescriptions for capsules containing strychnine sulfate 0.6 gr., arsenous acid 0.6 or 0.8 gr., and reduced iron 30 gr. to be distributed among 20 capsules. All the compounders added milk sugar to the mixture. From the weights of the contents of the individual capsules the following values for the average deviation and the maximum deviation, respectively, from the average weight were obtained for the different prescriptions: ±7.6% and ±21.0%; ±5.2% and ±14.3%; ±2.1% and ±6.0%; ±1.1% and ±3.3%; ±3.2% and ±7.2%. The results of the chemical analyses for the ingredients of these prescriptions are given in the same order as above in Table I.

The percentage variation from the theoretical total amount of each ingredient is shown. Note that sample No. 42-21, which showed the widest variations in the net weights of the individual capsules, was found to contain, in the bulk powder, the amounts of the ingredients most closely approximating the theoretical quantities. Also note that the worst offender with regard to tested ingredients (No. 44-1330) packed his capsules with a maximum variation of only ±7.2%.

A prescription for codeine sulfate 3 gr., caffeine citrate 1½ gr., aspirin 30 gr., nux vomica extract 1 gr., and belladonna extract 1 gr., to be distributed among 8 capsules, was filled and tested. The total weight found was 33.8 gr. which was 9.3% less than the theoretical weight of 36.5 gr. The average deviation from the theoretical weight per capsule was ±7.2% with none overweight. The greatest deviation was −12.3%. Analysis for codeine sulfate showed 2.8 gr. present or an error of −6.7%.

Another prescription called for phenacetin ½ dram, aspirin ½ dram, and codeine sulfate 4 gr., to

TABLE I—PERCENTAGE VARIATION IN CAPSULE INGREDIENTS

| *Sample No.:* | *42-21* | *42-24* | *42-25* | *43-360* | *44-1330* |
|---|---|---|---|---|---|
| INGREDIENT | % VARIATION | % VARIATION | % VARIATION | % VARIATION | % VARIATION |
| Arsenous acid | −5.0 | −17.5 | −8.3 | −26.3 | Absent |
| Strychnine sulfate | −3.3 | −25.0 | −15.0 | −20.0 | Absent |
| Reduced iron | −0.3 | +10.0 | −12.7 | −23.7 | +71.3 |

make 12 capsules. The total weight found was 60.3 gr. which was 9.4% less than the theoretical weight of 64 gr. The average deviation from the theoretical weight per capsule was ±5.7% with none overweight. The greatest deviation was −8.8%. Analysis showed the following variations: codeine sulfate −7.6%; phenacetin −13.3%; aspirin −10.7%.

Another prescription calling for codeine phosphate, caffeine citrate, aspirin, and phenacetin showed wide variations in all respects except in deviation from the average mean weight per capsule. Apparently a commercially packed capsule had been substituted.

Stewart[9] reported results of analyses of nine prescriptions for phenacetin 18 gr. and aspirin enough to make 60 gr., the mixture to be distributed among 12 capsules. Weights of individual capsules showed that four of the nine sets of capsules came within a tolerance of ±10% of the average weight. The worst showed a maximum deviation of 33.7% from the average weight. Four of the nine samples came within a tolerance of ±10% for phenacetin content; the others varying from 77.3% to 114.0% of the amount prescribed. Two samples came within a tolerance of ±10% for aspirin; the others varying from 74.2% to 158 7% of the amount prescribed. One pharmacist supplied a pre-packed capsule containing caffeine in addition to the two prescribed compounds. Stewart states that eight samples of capsules containing a mixture of caffeine citrate, acetanilid, and sodium bicarbonate, and twelve samples of capsules containing calomel and sodium bicarbonate were tested with results essentially the same as those obtained with the prescriptions for capsules discussed above.

Since the general practice is to weigh the packed capsule against an empty capsule as a tare, a degree of accuracy approaching the limits feasible in other forms of medication, e.g., tablets, are practically unobtainable for unit dosage by this procedure. This should not influence the preparation of the bulk powder to be distributed among the capsules. Analytical results based on the combined contents of the capsules supplied on prescriptions indicate that even here the variations often exceed a tolerance of ±10%.

## Powders

The following prescription was tested: Anesthesine 2 gr.; sod. phenobarb. 1/4 gr.; acetylsalicylic ac. and acetophenetidin 5 gr. of each per powder. Twelve powders. The total weight exceeded the prescribed weight by 16.7%. Seven of the twelve powders fell within a ±10% variation from the theoretical weight. Of the remaining five powders, the lowest weight was 27.6% below and the highest weight was 25.2% above the theoretical weight. The average deviation was ±12.6%.

The following prescription was tested: Solid ext. belladonna 2 gr.; sod. bicarb. and mag. oxide, of each 1 dr., to make 12 powders. The total weight varied from the prescribed weight by −15.7%. Ten of the twelve powders did not fall within a ±10% variation from the theoretical, the only high value being 10.3% above and the lowest value being 35.5% below the theoretical weight. The average deviation was ±17.4%.

Another prescription, similar to the preceding one except that 3, instead of 2, gr. of belladonna ext. were requested, was tested with the following results. The total weight varied from the prescribed weight by only +0.6%. All the powders fell within a ±10% variation from the theoretical. The average deviation was ±5.7%.

Stewart[9] analyzed four samples of prescriptions containing powdered sulfadiazine 40 gr. and enough lactose to make a total weight of 60 gr. of the mixture to be mixed and divided into 20 powders. The worst sample showed an average deviation of ±12.5% from the average weight and a maximum deviation of 34.7%; while the best showed an average deviation of ±7.3% from the average weight and a maximum deviation of 17.8%. The sulfadiazine content in the four samples varied from 92.5% to 103.0% of the amount prescribed.

## Present Procedure Inadequate

After a careful consideration of the problems involved in dispensing powders, only one conclusion can be reached. If the dispensing of powders is to be placed on a scientific level the following type of procedure must be followed:

1. Equipment must meet required standards.
2. Sufficient quantities of ingredients to make at least one powder more than the number prescribed should be weighed and thoroughly mixed.
3. A sufficient quantity of the mixture to meet the requirement for each individual powder should be weighed and transferred to the powder paper, or the paper could be tared and the powder weighed on it.

Unless this type of procedure is followed it is a waste of time to talk about setting a precise limit of tolerance in the filling of prescriptions for powders. For it is after the factors removed by this procedure are eliminated that the errors caused by carelessness and poor technique are comparable with those responsible for errors in filling prescriptions calling for liquid preparations. The same reasoning holds for the filling of prescriptions for capsules with the exception that each empty capsule must be tared before filling with the required weight of the prescribed ingredients.

It may be a waste of time to talk about getting all pharmacists to use a procedure like the one

indicated. Many pharmacists undoubtedly can do fairly accurate work using the generally accepted procedures. But there can be no doubt that many others cannot do so. As long as the present procedures are used, the extent of variations from the exact values in powder and capsule preparations prepared in the drugstore are going to be large, especially with regard to variations among the individual portions of the products.

## Liquid Preparations

Variations in compounding liquid preparations can be attributed mainly to the following factors:

1. Condition of medicinal substances (state of purity and official tolerances, hydration, etc.).
2. Accuracy of apparatus.
3. Personal factors.

At present, the only way factor 1 can be controlled by most pharmacists is by purchasing chemicals and other medicinal agents from reliable drug manufacturers and keeping the articles under proper conditions to prevent alteration as much as possible. Factor 2 has been discussed elsewhere in the paper. Factor 3 should have been taken care of in the course of the pharmacist's education.

Theoretically then, liquid preparations should be compounded with a greater degree of precision than could be expected of other types of medicinal preparations. Let us see if this is the case. Eight prescriptions for codeine sulfate and one for codeine phosphate in various syrupy vehicles were filled and tested. The results are given in Table II.

TABLE II—PRESCRIPTIONS CONTAINING CODEINE

| Lab. No. | Codeine Sulf. Prescribed in Gr. | Codeine Sulf. Found in Gr. | Difference in Gr. | % Error |
|---|---|---|---|---|
| 41-199 | 6 | 5.22 | 0.78 | −13.0 |
| 41-200 | 6 | 5.70 | 0.30 | −5.0 |
| 41-337 | 8 | 8.22 | 0.22 | +2.8 |
| 41-338 | 6 | 5.37 | 0.63 | −10.5 |
| 41-339 | 6 | 5.46 | 0.54 | −9.0 |
| 41-454 | 6 | 6.54 | 0.54 | +9.0 |
| 41-1132 | 6 | 5.85 | 0.15 | −2.5 |
| 44-394 | 8 | 7.61 | 0.39 | −4.9 |
| 45-51* | 6 (Phos.) | 4.83 | 1.17 | −19.5 |

* This sample also contained 26.3% more ammonium chloride than was prescribed.

The values given in Table II show an average deviation of ±8.5% in the codeine salt content.

Four prescriptions for 3% ephedrine hydrochloride were purchased and tested. Three preparations showed variations of +6.7%, −6.7%, and +6.7%. The fourth preparation showed a variation of −3.3%, but ephedrine sulfate had been substituted for the hydrochloride.

Results obtained with a number of prescriptions in which the amounts of the active medicinal agents in the solutions were determined are given in Table III.

TABLE III—PERCENTAGE ERROR IN PRESCRIBED SOLUTIONS

| Lab. No. | Ingredient | Amount Prescribed in Gr. | Amount Found in Gr. | Difference in Gr. | % Error |
|---|---|---|---|---|---|
| 40-1302 | Sod. Iodide | 120.0 | 115.2 | 4.8 | −4.0 |
| 40-1304 | Ammon. Iodide | 90.0 | 83.6 | 6.4 | −7.1 |
| 40-1308 | Sod. Iodide | 120.0 | 120.0 | 0.0 | 0.0 |
| 40-1309 | Ammon. Iodide | 90.0 | 89.4 | 0.6 | −0.7 |
| 40-1312 | Argyrol | 68.1 | 61.6 | 6.5 | −9.5 |
| 40-1313 | Argyrol | 68.1 | 68.6 | 0.5 | +0.7 |
| 41-153 | Pot. Iodide | 120.0 | 119.1 | 0.9 | −0.8 |
| 42-286 | Phenol | 180.0 | 152.0 | 28.0 | −15.5 |
| 42-287 | Phenol | 180.0 | 139.6 | 40.4 | −22.4 |
| 42-1081 | Phenol | 180.0 | 160.4 | 19.6 | −10.9 |
| 43-191 | Sod. Bromide | 360.0 | 374.9 | 14.9 | +4.1 |
| 46-281 | Protargol | 4.54 | 5.28 | 0.74 | +16.3 |
| 46-632 | Iodine | 23.1 | 21.6 | 1.5 | −6.5 |
| 46-632 | Pot. Iodide | 46.3 | 56.4 | 10.1 | +21.8 |
| 46-638 | Pot. Iodide | 454.0 | 345.4 | 108.6 | −23.9 |
| 46-679 | Boric Acid | 36.4 | 17.4 | 19.0 | −52.2 |
| 46-701 | Silver Nitrate | 45.4 | 44.5 | 0.9 | −2.0 |
| 47-303 | Silver Nitrate | 5.0 | 4.6 | 0.4 | −8.0 |
| 47-304 | Silver Nitrate | 5.0 | 5.0 | 0.0 | 0.0 |
| 47-305 | Silver Nitrate | 5.0 | 4.8 | 0.2 | −4.0 |
| 47-306 | Silver Nitrate | 5.0 | 4.8 | 0.2 | −4.0 |
| 47-307 | Silver Nitrate | 5.0 | 5.4 | 0.4 | +8.0 |

Stewart[9] reported results obtained with eight prescriptions for ammonium chloride 1 oz. and sufficient distilled water to make 4 fl. oz. The net volumes varied from 99.7% to 105.2% of the prescribed amount. Seven samples varied between 92.4% and 95.6% of the prescribed amount, a maximum variation of −7.6%. One sample contained only 73.6% of the prescribed amount of ammonium chloride, showing a variation of −26.4%.

Stewart also tested five prescriptions for phenol 0.65 Gm., magnesium sulfate 1.3 Gm., and sufficient glycerin to make 15 cc. He reports that the net volume varied from 86.0% to 102.0% of the amount prescribed. Phenol content showed a variation of −68.6% to −38.6% from the prescribed amount. Magnesium sulfate content showed a variation of −67.9% to −0.3%.

He does not give all the values and it is possible that the extremely wide variation with magnesium sulfate was caused by one very bad sample. This still leaves the poor results with phenol to be explained. After due consideration we must conclude that the reported results are nothing to cheer about.

## Ointments

Three prescriptions for ammoniated mercury 30 gr. and white petrolatum 1 oz. to be made into an ointment (510 gr. or 1.063 oz.) and two for ammoniated mercury 25 gr. (505 gr. or 1.051 oz.) were filled and tested. The results are shown in Table IV.

TABLE IV—OINTMENTS OF AMMONIATED MERCURY

| Lab. No. | Net Contents in Oz. (Apoth.) | Variation in Per Cent | $HgNH_2Cl$ Prescribed in Gr. | $HgNH_2Cl$ Found in Gr. | Difference in Gr. | Error in Per Cent |
|---|---|---|---|---|---|---|
| 42-20 | 0.68 | −36.0 | 30.0 | 32.0 | 2.0 | +6.7 |
| 42-285 | 0.74 | −30.4 | 30.0 | 35.2 | 5.2 | +17.3 |
| 42-288 | 1.61 | +52.4 | 30.0 | 26.3 | 3.7 | −12.3 |
| 42-293 | 0.90 | −14.4 | 25.0 | 20.7 | 4.3 | −17.2 |
| 42-638 | 0.92 | −12.5 | 25.0 | 20.3 | 4.7 | −18.8 |

The aim of the first three prescriptions was to prepare a 5.9% ointment of ammoniated mercury. The actual strengths of these ointments in the order given above were 9.8%, 9.9%, and 3.4%. The last two ointments should have contained 5.0% of ammoniated mercury. The concentrations found were 4.8% and 4.6%. It appears that the first two pharmacists dispensed ammoniated mercury ointment U. S. P. XI.

## Other Extemporaneous Preparations

In addition to the all too few prescriptions which are obtained for checking purposes many preparations are obtained from drugstores for routine check analyses. In Maryland, the drug inspectors are directed to obtain many extemporaneous preparations.

In these cases the pharmacist almost always knows that his preparation is being obtained for checking purposes. But, since he must compound the requested preparation, the operation is practically equivalent to filling a simple prescription. These preparations are required to meet existing standards if they are official galenicals. The others are allowed a tolerance of ±10%, except in unusual cases.

Experience has shown that there are certain extemporaneous preparations that will show a high percentage of samples outside the set tolerances. One of these is diluted hydrochloric acid. For one or more reasons, correctly preparing two fluidounces of this preparation seems very difficult, even when required apparatus is present.

Quite a few pharmacists apparently keep metric measuring utensils for no other reason than to comply with state regulations. If the directions for the preparation are given in the metric system they use less accurate utensils, and make a conversion from the metric to the apothecary system. What the introduction of a mathematical step will do, too frequently, to pharmaceutical accuracy is indicated by state board examination results and studies of prescriptions requiring such a step. It does no good. Furthermore, some pharmacists do not know that directions for the preparation of diluted hydrochloric acid are given in the U. S. P.

It follows that, whatever the cause, inclusion of a large number of such samples in any survey would show the pharmacist in the most disparaging light. On the other hand, there are samples which pharmacists seem to have little difficulty in compounding with a fair degree of accuracy. Naturally, a large number of such samples will lower the over-all percentage of variation.

Let me emphasize that the samples included in this survey were not selected to make the com-

(*Continued, page 561*)

BENADRYL PYRIBENZAMINE

# Antihistamine Drugs

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IT HAS been demonstrated that the release of histamine from the tissues is at least in part responsible for the symptoms of allergic manifestations. This has turned the attention of investigators to creating means by which the histamine would be made ineffective. Some have thought that injections of histamine would produce a tolerance to it; this has been pretty well disproved. The claim that the conjugated histamine (histamine-azo-protein or hapamine) would produce histamine tolerance has also been denied by most critical observers. The enzyme histaminase when incubated with histamine in the test tube destroys moderate amounts of the latter. However, when histaminase (torantil) is administered to the living animal or man it is ineffective.

Until recently the only effective methods of combating the histamine have been: (1) the relief of the symptoms produced by histamine by such drugs as epinephrine, ephedrine and aminophylline and (2) the immunizing injections of a specific antigen (for instance, pollen treatment), which develops a blocking substance interposing itself between the antigen (pollen) and sensitizing antibody, thus interfering with the allergic reaction. This method of immunization or desensitization is still the method of choice in the treatment of allergic disease. It offers more lasting effects and a more basic approach, and is not to be displaeed by the new drugs which we shall presently discuss.

In the last few years a rather intensive research has been going on for an ideal antihistaminic substance. The search has been directed mainly to the type of chemical which is structurally constituted to displace histamine from the cell. The amino acids histidine, arginine and cysteine were such agents, but were too weak in their antihistaminic activity and too toxic.

In France, Fourneau and his collaborators more than fifteen years ago began to synthesize new compounds displaying antihistaminic and antianaphylactic properties. Their first substances, however, were too toxic for clinical use. The first useful French compound was Antergan, which has now been replaced by the less toxic compound, Neoantergan (*N*-*p*-methoxybenzyl-*N*-dimethylaminoethyl-$\alpha$-aminopyridine).

In this country two antihistamine drugs have been placed on the market. These are benadryl ($\beta$-dimethylaminoethyl benzohydryl ether) and pyribenzamine(*N'* - pyridyl - *N'* - benzyl - *N* - dimethylethylenediamine). In addition there are many newer compounds which are now in the experimental stage and many of them are now undergoing trial by us. Some of these may be on the pharmacist's shelves in the near future. In this discussion, however, we shall consider mainly benadryl and pyribenzamine.

## Clinical Uses

Pyribenzamine and benadryl have been found to be useful in the symptomatic relief of a number of allergic conditions. It should be distinctly understood that none of the antihistaminic drugs is more than a palliative remedy. At best they relieve symptoms only for a few hours following the administration of each dose and seldom do they relieve all symptoms completely.

A large percentage of seasonal hay fever sufferers obtain some measure of relief from pyribenzamine. Although benadryl does not help as frequently as pyribenzamine, it is nevertheless effective in many patients. An individual patient may respond better to one particular drug than to another. In my experience with pyribenzamine more than 80% of the hay fever sufferers obtain benefit. In some the relief is moderate, in others it is marked. Those patients who have had desensitizing injection treatment respond much better to the antihistaminic drugs when they are needed. The milder cases are helped more than the severe cases, and those who are helped early in the season may not be helped as the season advances.

The first part of the ragweed season of 1947 was very mild and I can safely predict that some of

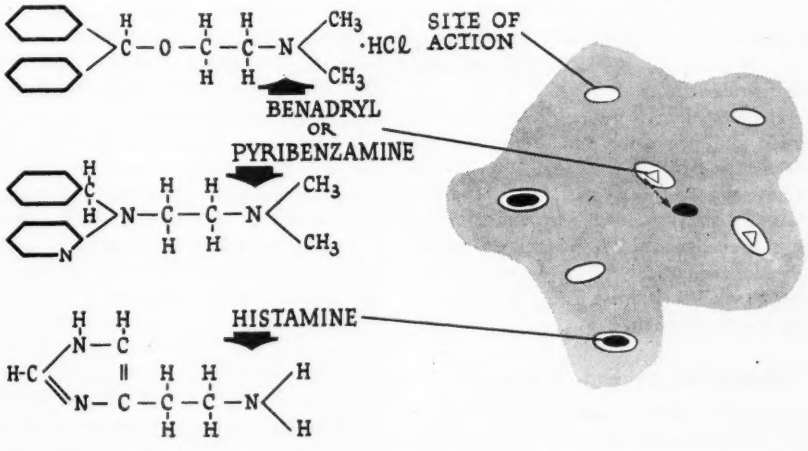
those hay fever sufferers who obtained relief from these drugs during that time will be greatly disappointed in heavier seasons. The symptoms benefited most are the tickling and sneezing. The nasal obstruction responds least and those who have obstruction as the major complaint may fail to receive material benefit.

It is important to note that about one-third of all seasonal hay fever patients have an associated asthma. In the majority the asthma does not respond to the antihistaminic drugs, although the pollen injections usually prevent this complication. The chronic perennial vasomotor rhinitis (year-round hay fever) responds pretty well to pyribenzamine, but not as well as the seasonal type.

Urticaria and angioneurotic edema are helped by benadryl or pyribenzamine in about 80% of the cases. The itching is the symptom most likely to be benefited while the swellings are more resistant. The reactions from penicillin, sulfonamides and other drugs respond well to the antihistaminic drugs. The itching of atopic dermatitis (eczema), pruritus ani and vulvae and some other types of itching is also frequently relieved. Here again it should be emphasized that these drugs are only of value for symptomatic benefit and that the duration of the disease is about the same as it would have been without the drug.

Unfortunately, an erroneous impression has been created among physicians that pyribenzamine and benadryl are the drugs of choice in the treatment of asthma. Every week I see patients who have been dosed for a long time with these drugs without effect against the asthma, whereas the substitution of ephedrine, aminophylline or iodides may produce marked improvement in twenty-four hours. The antihistaminic drugs have been of little value in the actual asthmatic state. Occasionally they may be of synergistic aid if combined with ephedrine or aminophylline. In the spasmodic allergic cough without dyspnea these drugs may be of some value.

These drugs have a high incidence of unpleasant side actions. In the usual therapeutic doses benadryl produces such symptoms in 50%




**THE MAJOR MECHANISM** of allergic reaction involves abnormal production of histamine in the tissues, according to present concepts. Research has been aimed at blocking the exaggerated histamine effects in allergy patients. Some compounds having a chemical structure similar to histamine are believed to unite with the same portions of the cell that would unite with histamine. Benadryl and pyribenzamine have this structural relationship (see formulas), and the concept of their antihistamine action is illustrated diagrammatically above.

Ordinarily histamine would be adsorbed by the sites of action in a receptive cell, producing physiologic histamine effects. When an antihistamine drug reaches the cell it is thought that, because of structural similarity to histamine, it replaces histamine at the site of action. Supposedly no particular physiologic action then occurs. The abnormal histamine metabolism causing allergic symptoms is thus brought under control. This may be considered as a competitive action: The benadryl or pyribenzamine enters some of the sites of action in the cell (as shown in the diagram) thus making them unavailable to histamine.

of the patients, while pyribenzamine affects 23%. The most common complaint is lassitude or sleepiness. This is more frequent and more severe with benadryl, but is also common with pyribenzamine.

While many patients are totally unaffected, the effect on others is so intense that they must forsake their activities and go to bed. Others who keep on their feet may be lacking in alertness, be unable to concentrate and may display defects in coordination. The potential dangers arising from such blunting of the sensorium and diminution in alertness in large numbers of persons are quite evident. This constitutes a very important problem for which the pharmaceutical manufacturer, the physician and the pharmacist must hold themselves responsible.

Other undesirable actions of these drugs may be dizziness, gastric irritation, loss of appetite, diarrhea, palpitation, nervousness, dryness of the mouth and throat and insomnia. In some instances the untoward effects may be obviated by substitution of another antihistaminic drug. In other instances the undesired effect may be combated by remedial drugs. For example, sleepiness might be treated by amphetamine or desoxyephedrine. However, the side reactions are so variable qualitatively and quantitatively that it would be next to impossible to counteract these effects efficiently and without producing other undesirable effects.

Several cases of more serious reactions have been noted, and the possible remote effects on the nervous system, blood, liver and other vital organs have not been yet determined. The frequency and variability of such toxic actions are enough of a challenge to the physician when he prescribes for his patient. Any pharmacist who is tempted to sell such drugs over the counter is certainly toying with danger.

## Administration and Dosage

Pyribenzamine is dispensed in 50-mg. scored tablets. The average dose is 50 mg., although many respond to 25 mg. and others require 100 mg. or more. The drug is also put up in the form of an elixir, 20 mg. to the drachm. Small children need 10 to 25 mg., while older children tolerate about the same doses as adults.

Benadryl is dispensed in 50-mg. and 25-mg. capsules and in an elixir containing 10 mg. to the drachm. The doses are about the same as for pyribenzamine, except that the larger doses are not tolerated as well.

The frequency of administration is about every four to six hours when the symptoms are continuous. In most cases, however, it is best to direct the patient to take the drug only when he needs it. Frequently this means only once a day or even once in several days.

There is a great deal of misunderstanding about the use of these drugs. From the nature of their action it is apparent that they should not be administered for hay fever prior to the onset of the hay fever season. When the antihistaminic drug is effective it is as efficient in relieving as in preventing allergic symptoms. In most allergic conditions it is neither necessary nor advisable to have the patient take the medication a number of times daily without regard for the presence or absence of symptoms. When administered under such conditions the drug is frequently given credit for producing benefit when the actual allergic symptoms would not have been present without the drug. The undesirable side actions and the possibility of producing drug tolerance are further arguments against the unnecessary use of these helpful agents.

Very early in our experience with these drugs we had shown that when they were applied locally they were effective in inhibiting the whealing and itching from histamine and locally applied allergens. This led me to think that such topical application might be useful in eczema and other itching skin conditions. After considerable preliminary trials we found that the most effective form was an ointment containing about 2% of pyribenzamine.

We have used chiefly two types of ointment: one with a petrolatum base, the other with a water-soluble base. The latter appears to be more desirable in most instances. This ointment may irritate highly sensitive or acutely inflamed skins, but is very useful in the subacute and chronic itching dermatoses. I understand that many pharmacists are filling the physician's prescriptions for this item by preparing an ointment in which the triturated pyribenzamine tablets are incorporated. At this writing the ointment has just been placed on the market by a manufacturer. I may add that a number of the other antihistaminic drugs can also be used for ointments.

## Other Antihistaminic Drugs

The field of antihistaminic drugs has attracted the attention of many pharmaceutical houses. The research chemists and pharmacologists of a large number of these industries are feverishly at work attempting to find a drug which will come closer to perfection in its activity and freedom from undesirable side actions.

Some manufacturers might of course be satisfied with a competitive product, even though it were no better than those now available. There is some justification for such an attitude. I have found that a particular drug having a lower therapeutic efficiency index than another may constitute the most effective drug for a particular person.

I have had the privilege of being on the ground floor of the investigation of a large number of these compounds in my experimental laboratory and in my practice. Sometimes this trust that the manufacturer has placed in me may prove embarrassing, as was the case with one identical drug which two manufacturers submitted to me, neither of them knowing for many months that the other had synthesized it.

The reader will understand that I cannot discuss the chemistry nor the experimental and clinical developments of the newer drugs. I may say that there are some interesting materials in our hands and that some of them will be introduced to the pharmacist in due time. If any reader has the notion that a new drug of this type is developed and readied for distribution in a fortnight or so, it should be dispelled by the following estimate of an average life cycle in development of a reliable compound of this type:

| | | |
|---|---|---|
| 1. | Preliminary experimentation and screening by chemists and pharmacologists | 2 years |
| 2. | Biologic investigation by manufacturer | 1 year |
| 3. | Experimental and clinical investigation by key expert or experts | 1 year |
| 4. | More general experimental clinical trial | 1 year |
| | Total | 5 years |

Some may take more and some much less time, but all require the above numerical procedures. Since my participation constitutes chiefly that encompassed in step number 3, it is not too difficult to foresee that the pharmacist's shelf should contain in a year or two still more effective prescription drugs for treating allergies.

# RxRxRxRxRx

## WIDER FIELD OF BENADRYL THERAPY STUDIED

DIPHENHYDRAMINE (Benadryl) and related drugs may have many unexplored uses. Results suggesting that the drug may gain a broader application in therapy were obtained in a study by Drs. L. S. Blumenthal and M. H. Rosenberg of George Washington University, Washington, D. C.

In a report on use of diphenhydramine to treat 140 cases of various allergic conditions, or states presenting similar symptoms, some of the most encouraging results were obtained in contact dermatitis. Although the series of patients was small, the physicians are of the belief that the drug will find a place in the treatment of contact dermatitis. Previous reports represent divided opinion concerning the value of such therapy. Of 16 patients treated by Blumenthal and Rosenberg 12 received pronounced relief and four were moderately improved.

Of 29 patients with hives, 24 received pronounced relief, one obtained moderate relief and four did not receive any significant relief.

Of 23 patients with seasonal hay fever, 15 received pronounced relief, five obtained moderate relief and three were not benefited.

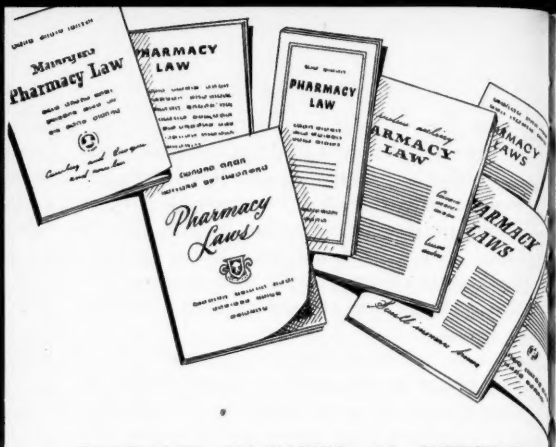
Of 11 patients suffering with migraine, four received pronounced relief, two obtained moderate relief and five received no relief.

Diphenhydramine did not prove particularly effective in bronchial asthma cases.

The drug was also given to a number of patients undergoing blood transfusions. Results, although inconclusive, were considered to suggest possible effectiveness of the drug in preventing transfusion reactions.

Treatment of various other conditions was reported but not evaluated because of the small number of patients in the series. The investigators conclude, however, that there should be more extended studies of the antihistaminic drugs in this field.

—*J. Am. Med. Assoc.*, 135: 25, 1947




**PHARMACY DIAGNOSED AS SUFFERING FROM LEGAL MALNUTRITION... PASSAGE OF RESTRICTIVE LAWS IS NEEDED IN INTEREST OF PUBLIC AND PROFESSION**

# NEED FOR MODERN PHARMACY LAWS

by **LESLIE D. HARROP**

GENERAL COUNSEL, AMERICAN DRUG MANUFACTURERS ASSOCIATION

PHARMACY appears to be suffering from legal malnutrition. This diagnosis is like one that an outside physician might give when brought into consultation on a case possessed of many puzzling aspects. It may well be that you, as the patient, will disagree entirely with the suggestion that anything is wrong. Nevertheless many of your own experts feel the patient is in need of some beneficial change.

This discussion will not be addressed to the precise therapy necessary to remedy the ailment. It will be an analysis of the factors considered and evaluated in coming to the conclusion that there is a real need for modern, strong pharmacy laws.

Carrying the simile a step farther, there are elements of the pharmaceutical profession who, like many other patients, just will not eat a correct diet. Other elements seem to find difficulty in synthesizing the foods ingested. More bluntly, there are portions of the profession who seem entirely indifferent to the long-range welfare of pharmacy so long as the profit side of the ledger is satisfactory today. Other elements are so anxious to keep their feet in the clouds that they refuse to recognize factors of serious danger to the very existence of the profession.

Pharmacy, one of the oldest of professions, is today regulated and presumptively protected by a patchwork makeshift of laws that have collected on the statute books of the several states over periods as long as a century.

Recognition of this problem is not claimed as new. For a number of years there has been increasing effort to recodify and modernize these laws. The AMERICAN PHARMACEUTICAL ASSOCIATION naturally has played a leading role in this work. But merely to draft an ideal bill manifestly is not enough. The bill must gain the approval of the legislature and become law to be of value.

First it might be well to pause and ask ourselves a question that will seem quite unessential when addressed to the members of this ASSOCIATION. Namely: "Is there a place left for the profession of pharmacy?"

Putting aside your momentary resentment that anyone in this day and age would pose that question, let us examine it. The profession of pharmacy is more intimately connected with trade and merchandising than is any other recognized profession. This change has come about gradually but surely through the years. We are not confusing the compounding of prescriptions and the sale of drugs generally in making that statement. Thought is being given to the vari-

Presented before the House of Delegates, AMERICAN PHARMACEUTICAL ASSOCIATION, 1947 meeting.

ety of merchandising efforts that go on day after day throughout the modern drugstore. A great many of these have little or no real connection with the profession but have proved to be profitable lines of merchandising.

So to the extent that a pharmacist is thus engaged we will have to admit that the profession is not a requisite. If illustration be needed, let us point to the soda fountain, the cigar counter, and the non-drug sundry and notion business that has pervaded the drugstore of today. Furthermore there is a trend today toward establishment of so-called "super" stores that more nearly resemble a department store than the drugstore or pharmacy of tradition.

Thus we find that a fair portion of the activities of the professional pharmacist is directed to other than pharmaceutical pursuits in many cases. Naturally this has invoked commercial rivalry from businesses of a similar character over these sidelines. It would be expecting less than normal human responses to consider it other than natural that restaurant owners would resent the drugstore lunch counter business, that cigar store owners would consider themselves the natural rivals of the drugstore cigar counters, and on ad infinitum.

One or both of two things usually happens in such cases. Competition may manifest itself by sharpened activity along the line undertaken by the drugstore or the other store may undertake a digression into the fields normally served only by the pharmacist.

Before exploring this more fully, let us return for a moment to our question as to the continued need for the profession of pharmacy.

Every profession has been created based upon a public need for experts in that field. To protect the public from imposition by persons pretending to possess the qualifications of such experts, laws are passed setting forth minimum standards of education and training that must be possessed by those entitled to hold themselves out as members of the profession. Thus we have formed a legal monopoly. Medicine, law, pharmacy and other recognized professions have been granted a monopoly in the privilege of their practitioners to perform certain skilled services for which they have been specially trained.

Unless, however, the law does grant a real and genuine monopoly in these fields of skill, newcomers will not be attracted to the profession and in time it will cease to exist.

We must remember that in using the words "legal monopoly" we are talking about one created by law for the benefit of the public at large. It is necessary that the public, for example, be protected in going to a person holding himself out as a physician by first being assured that he is well trained for his work and, second, that he, and only persons so qualified, can so serve the public. Likewise in law. And the same in pharmacy.

## A Continuous Struggle

No profession has ever existed that did not struggle continuously to improve the standards of its own services. Nor did a profession ever exist that has not had to fight continuously against encroachment by those who would reap the rewards paid to those possessed of the superior skill but without incurring the expenses of time and money in qualifying for such services.

To prove that pharmacists do not have a unique problem in this respect, we can look to the constant litigation against those who try to practice the healing arts without proper training for such services. Lawyers are constantly battling against the encroachment of individuals and corporations seeking to sell legal services for a profit without the prerequisite preparation for and admission to the bar.

So aside from the purely commercial avarice created by the expansion of drugstores into foreign fields, there is an increasing desire to trespass upon the field carved out by law for phar-

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### ABOUT THE AUTHOR

*Leslie D. Harrop (shown in the photograph on the facing page) was born at Ashland, Kentucky, in 1901. He is a graduate of Albion College (Michigan) and the University of Detroit Law School. Prior to engaging in legal work in the pharmaceutical field, Mr. Harrop served as assistant attorney general of Michigan and as chief counsel to the Michigan State Banking Department.*

*He is now general counsel for the American Drug Manufacturers Association and also general counsel for The Upjohn Company. In these capacities and as a delegate to the National Drug Trade Conference, Mr. Harrop has gained a broad background upon which to base the accompanying discussion of the practicing pharmacist's position in relation to the need for modernized pharmacy laws.*

*The author is a member of the State Bar of Michigan, American Bar Association, New York State Bar Association and the American Judicature Society.*

macy. Too frequently the law is inadequate in properly defining this field.

We have seen grocery stores try to invade the field of drug sales by attempts to market vitamin preparations in pharmaceutical form. So far these efforts have failed. Pharmacy cannot, however, thank the law for protecting it from this incursion. The failure was a direct result of public refusal to buy from grocers. There was almost universal realization of the fact that only the pharmacist is qualified to dispense such products.

There is, however, an ever-increasing easing into this field as more and more news counters, eating places, cigar stands and the like offer headache remedies, antacids and other drugs for common ailments. Most of this can be traced back to hopelessly outdated and inadequate pharmacy laws.

Recognizing all of these trends as matters of rather common knowledge, it becomes desirable to inquire further and see if in addition there are any other factors that bear upon this all-important issue of securing the enactment of modern, effective and strong pharmacy laws.

## Against Powerful Opposition

Certainly along this line it is necessary to recognize that there is always powerful opposition to the restrictive character of a well-drafted pharmacy law. This observation is made with no intention of arguing with such groups the correctness of their position from their viewpoint. We are not considering in this relation the familiar and wholly logical exceptions to be found in most pharmacy laws for sales of certain common household remedies by general stores remote from pharmacies or drugstores. This is a matter of furthering the protection of the public, which is the chief aim of the pharmacy law. But these opposition pressure groups seek to widen this breach and build up a general exemption from exclusive sale in the drugstore of an ever-increasing number of drug products.

Carried to its quite logical conclusion the efforts of these groups, if successful, will within a short time leave the prospective pharmacist with the dubious distinction of being able to say he is the only person who can fill prescriptions. And he will also realize that without a day of training in pharmacy John Jones, who had the minimum amount of common schooling, can sell in the corner grocery store about ninety-five per cent of the medicines used by the public.

These efforts in opposition to passage of new pharmacy laws are not confined to the cloakrooms of the legislatures. Clever advantage is taken of all angles offered by all related laws.

Such opposition can be summed up as a desire to ride with the horses and run with the hounds. Those who seek to broaden the exemptions from the restrictive features of the pharmacy laws are most desirous of the friendship and cooperation of the pharmacist. But we submit that self-interest often causes them to fall short of true friendship that should have the genuine well-being of the profession at heart.

What are some of the collateral forces that have a bearing upon this important matter?

## FDA—Two Administrations

In Washington we have the Federal Food and Drug Administration. Do not anticipate my remarks improperly. I am not going to say or insinuate that this fine governmental body is a party wittingly to anything detrimental to the pharmacist. Certain of their activities, however, definitely can have that effect if they are allowed to be twisted and turned for that purpose.

In the first instance, since its inception in 1906 with the passage of the Wiley Pure Food and Drug Act, that agency has always been directed by individuals more concerned with foods than with drugs. This is rather logical when you consider the enormous size of the food industry compared to that of the drug industry. Dr. Wiley, Mr. Campbell and the present Commissioner, Dr. Dunbar, were and are men well trained in their fields. There have been from time to time very able men as head of the Drug Division of the Food and Drug Administration, but always there has been at the top a man more concerned with food than with drugs. Sometimes it has been a bit disheartening to sit down to discuss the difficult and grave task of controlling important drugs only to find top officials of the Food and Drug Administration, in groping for comparisons, talking in terms of canned peaches or canned shrimp.

It would seem wholly logical and for the best interests of all concerned if the head of drug control in the Federal government should be a man trained in pharmacy who has that field as his principal interest. Maybe this would require splitting the Food and Drug Administration into a Food Administration and a Drug Administration. This should not be too difficult, however, since both would be but arms of the Federal Security Agency.

Whatever the means used to gain more pharmacy-conscious control from Washington, it

has a strong bearing upon the principal issue here because the present law presents difficulties of interpretation in these conflicting fields. Much of the support claimed by the grocery group trying to break into the vitamin market was from the ruling of the Food and Drug Administration that such products were subject to the control of the special dietary foods section of the law. Maybe the courts ultimately will say this was the intent of Congress but one can be permitted to wonder if the same ruling would have been made if drugs were being controlled by a separate arm of the agency freed from foods.

Let me again emphasize that this is neither criticism of the men heading that agency nor an expression of doubt as to the sincerity of purpose back of the rulings discussed.

It is of importance, however, as another piece in the pattern of what is to become of pharmacy. If we now strip from the pharmacist his right to control the sale of nutritional pharmaceutical products by vaguely defining them as foods, we have further narrowed the exclusive field granted him by his profession.

Then there is another queer quirk of circumstances where, as they often say of courts, hard facts make bad law. Under the Food, Drug, and Cosmetic Act in section 502 (f), requirement is made that drugs be sold under labels bearing adequate directions for use. Power is granted, however, to make exemptions from this requirement where such provisions are not necessary to protect public health. Originally the regulations permitted marketing of any drug under the exemption provision if it was labeled "Caution: To be used only by or on the prescription of a physician." Later under two different pressures this was modified. First some pharmacists complained that a labeling burden was placed on them by the exemption. Secondly the Food and Drug Administration was faced with an enforcement problem that defied their attempts at solution. They did not feel they were effectively controlling such products by limiting them to prescriptions or seeing that the pharmacist relabeled them in a satisfactory manner.

## A Look at the Record

Because of this double pressure the regulations were modified, and today all drugs except those too dangerous for lay use are required to bear adequate directions.

Turning to the *Congressional Record* to seek the intent in the enactment of the Food, Drug, and Cosmetic Act, you find such statements as: "The Act was not made for experts nor is it intended to prevent self-medication; it was enacted to make self-medication safer and more effective; and to require that drugs moving in interstate commerce be properly labeled so that their use as prescribed may not be dangerous to the user." Neither in this statement or elsewhere in the *Record* will you find any indication that this Act was intended to drive the patient from the physician and make him seek refuge in self-medication. It was not intended to extend or promote self-medication. It was aimed at making self-medication, when undertaken, a safer method of treating disease by giving to the layman who chooses to be his own doctor better information concerning the properties of the drug he proposes to use.

## Veering from the Intent

From such intent, however, these new regulations have veered sharply. Instead of a law to assure adequate labeling, it has been twisted into a law to promote self-medication.

Regardless of the desire of an ethical drug manufacturer, of a pharmacist or of the physician for products labeled to be used as directed by the physician, these new regulations require adequate directions.

No court challenge has been made directly upon these regulations to date. The American Drug Manufacturers Association protested their enactment vigorously. A recent California case held that "to be used as directed by the physician" was an adequate direction but we do not yet know whether this is a judicial trend that will prevail.

Under this set of circumstances and with this background, those who seek to increase the exemptions from the restrictive provisions of the pharmacy laws took advantage of the confusion to proclaim that there exist today only two types of drugs, to wit, those to be sold as packaged medicines across the counter and those limited to prescription. This was carried even further in an attempt to prove that there today remain no distinguishing characteristics between an "ethical" drug and a "proprietary" drug. This latter contention can be readily dismissed as wishful thinking.

The former contention cannot be dismissed so lightly. Whether so intended or not, such construction could well mean that every drug, except those restricted to prescription sale, would be placed in the same category. Thus if the pharmacy law has exemption for the sale of pack-

aged medicines it might well be held to encompass ninety-five per cent of the drugs in general use today.

### Is There a Place for Pharmacy?

Having examined a number of apparently remotely related matters and seeing how well they dovetail into a pattern of opposition to the proper type of pharmacy law, possibly we have reached the point where we can give positive answer to the original question of: "Is there a place left for the profession of pharmacy?"

Of course and naturally there is a demand for the profession of pharmacy. But that demand must be coordinated with strong restrictive laws that give to the pharmacist the exclusive right to practice his profession for the betterment of mankind.

Such laws must be passed over growing attempts to dilute them with exceptions in favor of the butcher, the baker and the candlestick maker. You cannot have continuance of pharmacy based upon a sole and exclusive right to fill prescriptions.

If the pharmacist is to meet continued and growing competition from the grocer by way of defining nutritional drugs to be foods and if packaged medicines are to be salable by everyone, you are no longer going to be able to induce an appreciable number of young men and women to spend four years in a pharmacy college preparing themselves for a profession of such limited advantages.

We submit that the labeling burden imposed under the former regulations on prescription items is one that the pharmacist should have welcomed. It was a burden imposed upon him by virtue of his profession. It distinguished his right and ability to sell drugs from that of the untrained and unlicensed layman. It is extremely regrettable that it was ever considered a burden for truly it was not a burden in any greater sense than that the care of a patient is a burden upon the physician and that the handling of legal matters for a client is a burden upon the lawyer.

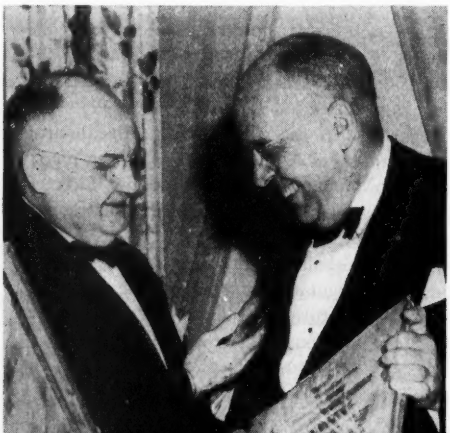
### Responsibilities Go with Privileges

Responsibilities go with these privileges granted the professions. As this ASSOCIATION bends every effort to seek passage of these new laws to safeguard its professional future, let it ever be mindful of the burdens cast upon it by the public in return for these benefits to be conferred by such laws.

If there be any exceptions to the rule that drugs shall be sold only in drugstores, let it be confined properly to instances where geographical remoteness from a drugstore warrants permission for a general store to carry a limited number of common household drugs and drugs for emergency use.

Discount the public support of many of these trends that have been enumerated. Remember that the public refused to turn away from the pharmacist in the purchase of vitamins. Reward that faith and respect of the public for the profession by serving it well and dutifully and by insisting vigorously that the profession of pharmacy, and that profession alone, is the one and only one qualified to dispense drugs of every character.

## G. D. BEAL CITED FOR SERVICE



A citation for service to pharmacy with distinction was presented to Dr. George D. Beal (right in photograph), A. PH. A. council chairman and assistant director of the Mellon Institute for Industrial Research, by the New Hampshire Pharmaceutical Association at its 74th annual meeting. Dr. George A. Moulton (left), executive secretary of the N. H. P. A. and vice-chairman of the A. PH. A. council, made the presentation and also bestowed upon Dr. Beal the gold medallion denoting honorary membership in the state association.

LILLY DIGEST . . .

# OPERATING STATEMENTS OF 1946

EVIDENCE that the upward trend in prescription practice is continuing and that in 1946 pharmacists on the average were more prosperous than ever before appears in the annual study of operating statements made by Eli Lilly and Company. In the publication just issued, the *Lilly Digest for 1946*, data from 1096 retail pharmacies are analyzed, of which 678 supplied separate and specific figures on operation of the prescription laboratory. The average costs, margins and profits of these 678 pharmacies are shown in Table I, classified according to the daily volume of prescription practice. A number of significant conclusions can be drawn from a study of the table. Some of these are:

**1.** The percentage amount of the gross margin rises with an increase in the proportion of prescription receipts to total sales. Thus, for each dollar from total sales the pharmacy owner has a larger proportion available for the payment of operating costs and for profit on the investment he has made in his pharmacy.

**2.** The percentage of the receipts paid for expenses rises with an increase in the ratio of prescription receipts to total sales. This increase is not as rapid as the rise in average gross margins.

**3.** Therefore, the average profit per dollar of sales rises with an increase in the ratio of prescription receipts to total sales.

**4.** The value, at cost, of the pharmacy's stock goes up with an increase in the ratio of prescription receipts to total sales. This rise in the value of stock on hand takes place at almost exactly the same rate as the rise in sales.

**5.** Therefore, the average rate of turnover of stock in pharmacies with the highest proportion of prescription receipts to total sales is almost exactly the same as for pharmacies filling a smaller number of prescriptions.

**6.** The ratio of prescription department stock increases with an increase in the ratio of prescription receipts to total sales. This increase in prescription department stock is not as great as the increase in prescription receipts per pharmacy.

**TABLE I—AVERAGE COSTS, MARGINS AND PROFITS OF PHARMACIES COMPOUNDING IN 1946—**

| | 1 to 5 prescriptions daily | 5 to 10 prescriptions daily | 10 to 20 prescriptions daily | 20 to 40 prescriptions daily | 40 and up prescriptions daily |
|---|---|---|---|---|---|
| Sales | $41,779—100.0% | $50,862—100.0% | $60,421—100.0% | $70,693—100.0% | $113,224—100.0% |
| Cost of stock sold | 29,177— 69.8% | 35,736— 70.3% | 41,139— 68.1% | 46,827— 66.3% | 72,104— 63.7% |
| Gross margin | $12,602— 30.2% | $15,126— 29.7% | $19,282— 31.9% | $23,866— 33.7% | $ 41,120— 36.3% |
| Total expenses | 9,433— 22.6% | 10,970— 21.5% | 13,967— 23.1% | 17,198— 24.3% | $ 29,062— 25.7% |
| Net profit | $ 3,169— 7.6% | $ 4,156— 8.2% | $ 5,315— 8.8% | $ 6,668— 9.4% | $ 12,058— 10.6% |
| Value at cost of general stock | $7015 | $8026 | $9110 | $10,443 | $16,521 |
| Value at cost of prescription department stock | $1051 | $1611 | $2073 | $3121 | $5333 |
| Prescription receipts | $1292 | $3228 | $6831 | $12,945 | $32,891 |
| Number of prescriptions filled | 1010 | 2583 | 5318 | 9402 | 24,669 |
| Average fee for prescriptions | $1.28 | $1.25 | $1.28 | $1.38 | $1.33 |
| Annual rate of turnover of general stock | 4.2 times | 4.5 times | 4.5 times | 4.5 times | 4.4 times |
| Percentage of prescription department stock to total stock | 15.0% | 20.1% | 22.8% | 29.9% | 32.3% |
| Percentage of prescription receipts to total sales | 3.1% | 6.3% | 11.4% | 18.3% | 29.0% |
| Percentage of prescription-sales dollar to each dollar invested in prescription stock | $1.28 | $2.00 | $3.30 | $4.15 | $6.17 |
| Average net profit per dollar invested in all stock | $0.45 | $0.52 | $0.58 | $0.64 | $0.73 |

TABLE II—DISTRIBUTION OF 678 PHARMACIES BY SIZE OF CITY AND NUMBER OF PRESCRIPTIONS FILLED

| POPULATION | PRESCRIPTIONS COMPOUNDED DAILY | | | | |
|---|---|---|---|---|---|
| | 1 to 5 | 5 to 10 | 10 to 20 | 20 to 40 | 40 and up |
| Under 5000 | 53% | 34% | 41% | 32% | 23% |
| 5,000 to 20,000 | 8% | 20% | 18% | 21% | 42% |
| 20,000 to 50,000 | 9% | 10% | 7% | 16% | 17% |
| 50,000 to 100,000 | 5% | 12% | 7% | 5% | 5% |
| 100,000 to 500,000 | 13% | 14% | 15% | 17% | 13% |
| Over 500,000 | 12% | 10% | 12% | 9% | 0% |
| Total | 100% | 100% | 100% | 100% | 100% |

**7.** Consequently, the ratio of the prescription-sales dollar to the dollar invested in prescription department stock is more than five times as great in pharmacies filling upward of 40 prescriptions daily as it is in drugstores which fill an average of no more than 5 prescriptions daily.

**8.** There is a steady rise in the average net profit per dollar invested in all stock carried by the pharmacy with an increase in the proportion of prescription receipts to total sales.

It will be noted from Table I that in pharmacies filling an average of no more than 5 prescriptions daily in 1946, prescriptions receipts for the year were $1292. The value at cost of prescription department stock was $1051. Assuming a gross margin of 50% the average rate of turnover of prescription stock would be only once every twenty months In the pharmacies studied which filled 40 or more prescriptions daily, prescription receipts averaged $32,891. The prescription department stock amounted to $5333 per pharmacy. If we again assume an average margin of 50% the rate of turnover on prescription stock is once every four months. This fact reflects the marked advantage of developing prescription practice. It is also evident that in a pharmacy with prescription receipts of only $1292 a small amount of the pharmacist's time will be occupied in supplying this professional service. On the other hand, prescription receipts of $32,891 are sufficient to keep one or more pharmacists occupied exclusively in the prescription laboratory.

Table II shows the distribution of the 678 pharmacies by size of city and number of prescriptions filled.

A further analysis of average volume of daily prescription practice on the basis of geographical distribution is shown in Table III.

There is no evidence in the Lilly report to support the contention of some pharmacists that the time, effort and funds devoted to a prescription laboratory are out of proportion to the income obtained. The Lilly studies over the past fifteen years have repeatedly demonstrated that the contrary is true. A rise in the proportion of prescription receipts to total sales results in an increase in income and profit of an even larger amount.

The 1946 Lilly study again indicates that there is no basis for a belief that prescription practice reaches a markedly high peak during only a few winter months. In the 678 pharmacies reporting, prescription practice on the average was at a minimum during June and July but was only 16 to 17% below the peak period of January. All

TABLE III—GEOGRAPHICAL DISTRIBUTION OF PHARMACIES BY NUMBER OF PRESCRIPTIONS FILLED IN 1946

| | PRESCRIPTIONS COMPOUNDED DAILY | | | | |
|---|---|---|---|---|---|
| | 1 to 5 | 5 to 10 | 10 to 20 | 20 to 40 | 40 and up |
| New England States | 3% | 11% | 9% | 7% | 10% |
| Middle Atlantic States | 6% | 18% | 22% | 17% | 11% |
| East North Central States | 47% | 30% | 15% | 14% | 10% |
| West North Central States | 21% | 18% | 13% | 21% | 11% |
| South Atlantic States | 1% | 5% | 7% | 6% | 16% |
| East South Central States | 0% | 0% | 3% | 8% | 11% |
| West South Central States | 3% | 6% | 10% | 11% | 16% |
| Mountain States | 10% | 11% | 9% | 4% | 1% |
| Pacific States | 9% | 1% | 12% | 12% | 14% |
| United States | 16% | 17% | 31% | 21% | 15% |
| Canada | 20% | 20% | 40% | 17% | 3% |

other months were only 3 to 12% below the maximum January volume of prescriptions. Month to month variations in the number of prescriptions filled were not significantly affected by geographical location. There was also little variation from month to month in the number of prescriptions filled when the pharmacies were grouped by the size of cities in which they are located.

In 1946 and other years the Lilly analyses of pharmacy operations revealed that quite a number of pharmacists do not keep a record of the number of refilled prescriptions. The *Lilly Digest* points out that this is a mistake since failure to keep a record of prescription refills is likely to result in a marked underestimate of the income and profit from the prescription laboratory. On the basis of this study it appears that for every 100 prescriptions filled in 1946, about 60 were new prescriptions and 40 were prescriptions that were refilled. There was no consistent variation in the proportion of refilled prescriptions to total prescriptions when the reports were tabulated according to size of city. A month to month comparison shows that the ratio of about 60 new prescriptions to 40 refills is maintained throughout the year.

**TABLE IV—GEOGRAPHICAL VARIATIONS IN AVERAGE PRESCRIPTION FEES**

| | |
|---|---|
| New England States | $1.26 |
| Middle Atlantic States | 1.26 |
| East North Central States | 1.41 |
| West North Central States | 1.32 |
| South Atlantic States | 1.19 |
| East South Central States | 1.12 |
| West South Central States | 1.23 |
| Mountain States | 1.52 |
| Pacific States | 1.54 |
| United States | 1.33 |
| Canada | 1.30 |
| Average | 1.33 |

A study of the average prescription fees reflects income from professional service as well as price of materials, which again demonstrates the importance of prescription volume. Table IV shows the geographical variations in average prescription fees in 1946, which range from the lowest average of $1.12 in the East South Central states to an average of $1.54 in the Pacific states. The over-all average for the group of pharmacies reporting was $1.33. Table V shows the variations in average prescription fees by size of cities.

A special study was made of a group of 199 pharmacies which made detailed reports both in 1945 and 1946. The figures on prescription receipts are shown below:

**TABLE V—VARIATIONS IN AVERAGE PRESCRIPTION FEES BY SIZE OF CITY**

| | |
|---|---|
| Under 5000 population | $1.21 |
| 5000 to 20,000 | 1.56 |
| 20,000 to 50,000 | 1.33 |
| 50,000 to 100,000 | 1.40 |
| 100,000 to 500,000 | 1.50 |
| Over 500,000 | 1.37 |
| Average | 1.33 |

| | 1946 | 1945 | Per Cent Increase 1946 over 1945 |
|---|---|---|---|
| Average prescription receipts per pharmacy | $11,389 | $9247 | 23.2% |
| Average number of prescriptions per pharmacy | 8640 | 7603 | 13.6% |
| Average price for each prescription | $1.32 | $1.22 | 8.2% |
| Per cent prescription receipts to total sales. | 17.4 | 16.6 | 4.8% |

Data on the over-all operations of these same pharmacies in 1945 and 1946 show that during the year there was a 17.7% increase in sales, 19.1% increase in cost of stock sold, and an increase of 15% in the gross margin. Total expenses increased 18.5%. In 1946 the average net profit went up 7.8% over 1945. The Lilly analysts conclude that there is a relationship between the above average profits in the 199 pharmacies and the increase in prescription receipts.

In addition to the 678 pharmacies reporting in detail on prescription practice there were 418 submitting operating statements only on the over-all operations.

For the total of 1096 pharmacies, sales reached a new high in 1946, averaging $69,422 for the year. This represents an 11.9% increase over 1945 sales figures. The details of average costs and net profit, with a comparison between 1946 and 1945, are shown in Table VI.

The net profits earned by these 1096 pharmacies expressed in percentage is given below:

41% earned a net profit of over 10% of sales.
30% earned a net profit of 5 to 9% of sales.
14% earned a net profit of 2 to 4% of sales.
8% earned a net profit of less than 2% of sales.
7% operated at a loss.

The average profit of $5951 per pharmacy in

TABLE VI—AVERAGE COSTS AND PROFITS OF PHARMACIES IN 1946 AND 1945

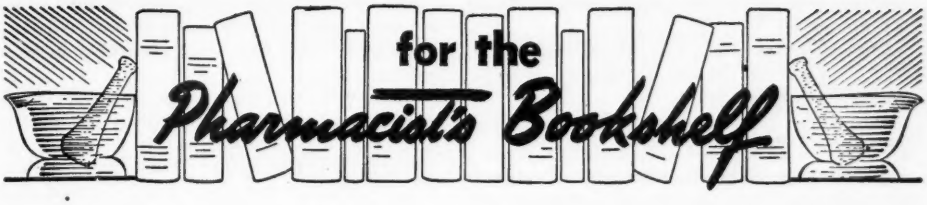
| | 1946 | | 1945 | |
|---|---|---|---|---|
| Sales | | $69,422—100.0% | | $62,038—100.0% |
| Cost of stock sold | | 46,995— 67.7% | | 41,565— 67.0% |
| Gross margin | | $22,427— 32.3% | | $20,473— 33.0% |
| Expenses: | | | | |
| Proprietor's or manager's salary | $4590—6.5% | | $4342—7.0% | |
| Employees' wages | 6270—9.0% | | 5273—8.5% | |
| Rent | 1950—2.8% | | 1860—3.0% | |
| Heat | 270—0.4% | | 245—0.4% | |
| Light and power | 475—0.7% | | 372—0.6% | |
| Taxes (except on building, income, and profit) and licenses | 418—0.6% | | 498—0.8% | |
| Insurance | 264—0,4% | | 195—0.3% | |
| Interest paid | 60—0.1% | | 61—0.1% | |
| Repairs | 195—0.3% | | 253—0.4% | |
| Delivery | 118—0.2% | | 64—0.1% | |
| Advertising | 413—0.6% | | 311—0.5% | |
| Miscellaneous | 905—1.3% | | 684—1.1% | |
| Estimated total depreciation except on buildings | 352—0.5% | | 251—0.4% | |
| Bad debts charged off | 63—0.1% | | 59—0.1% | |
| Telephone | 133—0.2% | | 128—0.2% | |
| Total expenses | | $16,476— 23.7% | | $14,596— 23.5% |
| Net profit | | $ 5,951— 8.6% | | $ 5,877— 9.5% |
| Value at cost of stock | | $10,487 | | $ 9,459 |
| Annual rate of turnover of stock | | 4.5 times | | 4.4 times |

1946 was only $74 more than in 1945, or, percentagewise, 1.3%. This is remarkably small in view of the fact that sales increased $7384 per pharmacy on the average, or 11.9%. The *Lilly Digest** points out that these figures show the very great effect on profits of small changes in gross margins and operating expenses. Compared with the sales increase of 11.9% the increase in the average gross margin was 9.5% in 1946 over 1945. With regard to operating expenses, it may be seen from Table VI that there was an increase of $1880, or 12.9%, in 1946 over 1945—more than the percentage amount of sales increase

This reflects an unusual situation, since a rise in total sales in a pharmacy ordinarily is accompanied by a drop in the percentage amount of receipts paid out for expenses. The increased 1946 expenses are due to several factors. Payments to employees were up almost $1000 on the average. The percentage of receipts used for this purpose rose from 8.5% in 1945 to 9% in 1946. The average amount paid for rent increased slightly during this same period from 2.8% to 3%, but rent did not advance as fast as sales. It was considered significant that the incidental or miscellaneous costs—such as lights, taxes, insurance, repairs and advertising—took a total of 5.4% of receipts in 1946 as against only 5% in 1945. Ordinarily such expenses would not increase much with a rise in sales, but they actually went up $545, or an average of a little more than $10 per week. It was pointed out that this calls for additional vigilance concerning thousands of small individual expenditures.

Pharmacy stocks rose 10.9% from 1945 to 1946, which was a little less than the sales increase. In general, stocks were kept to a figure in 1946 more consistent with present volume of sales than was true during the past few years. It should be remembered, however, that any purchases for more than current needs are speculative purchases, and especially so at this time.

* A copy of the complete *1946 Lilly Digest*, or information concerning the Lilly Analysis Service offered to pharmacists, may be obtained by writing to Eli Lilly & Co., Indianapolis 6.




### PUBLIC RELATIONS IS NOT PRESS AGENTRY

The press-agent approach to public relations is perhaps typified by P. T. Barnum's comment: "I don't care what you say about me, just so you mention my name." We recall an example of this a few years ago when a public relations endeavor finally resorted to crowning a leggy "Pharmacy Queen" to achieve its quota of publicity.

How far stunt publicity ordinarily will be from a sound public relations program becomes clear from a reading of *Public Relations: Principles and Procedures*. The authors appear to know whereof they speak and have a record of achievement in the public relations field.

This book has little to recommend it for the practicing pharmacist. It is primarily a primer—and an excellent one—for the student of public relations and those who have made this field their profession. But it should be worth while for executives of pharmaceutical associations, their public relations committees, and the business administrator who must deal with the press or public relations counsel.

Much of the book is given over to a discussion of public relations as a profession and the counsel's methods and his relations with the client. Of particular interest to the field of pharmacy, however, are the chapters on trade associations and publicity techniques. The latter includes a brief commentary on convention public relations. The book also relates how well-planned public relations overcame the effect of unfavorable incidents in the history of McKesson and Robbins and the makers of Castoria. The success with which the American Dental Association used public relations tools to fashion greater prestige for the profession is also recorded.

PUBLIC RELATIONS: PRINCIPLES AND PROCEDURES—Theodore R. Sills and Philip Lesly—*Richard D. Irwin, Inc.*, Chicago; 321 pp., $3.75.

### GUIDE TO HEALTH ORGANIZATION IN THE U. S.

*Guide to Health Organization in the United States* is designed to supply a ready-reference outline of the increasingly complex network through which Americans receive health service. The cooperative and interrelated activities of private, voluntary, and public (local, state, and national) agencies represent a confusing pattern to the uninitiated and sometimes to health workers themselves. The booklet makes an able attempt to clarify this picture for the public, the student and health workers. That "the result is a panoramic view of the entire health structure of our nation," as stated in the foreward, might be questioned by the pharmacist who notes that his profession is conspicuous chiefly by its absence from the text.

Neither pharmacy's professional organizations nor its practitioners will be found among the outlines of the nation's health structure. That there are pharmacists who serve with the U. S. Public Health Service is recognized in an enumeration of that agency's commissioned personnel. And in a table showing the relative frequency with which different types of state agencies have responsibility for specified health activities, there is an interesting comparison of the licensure agencies for the various health professions, including pharmacy.

Although the *Guide* discusses private and voluntary agencies in a way to orient the reader to the over-all structure of health organization, it appears most helpful in delineating the functions of public health services at the Federal, state, and local levels. The tables, appendices, and bibliography add to its usefulness as a reference. This booklet will be of particular interest to officials of state pharmacy boards, organization officials, health councils and the like.

GUIDE TO HEALTH ORGANIZATION IN THE UNITED STATES (Miscellaneous Publication No. 35)—Joseph W. Mountin and Evelyn Flook, U. S. Public Health Service—*Superintendent of Documents*, U. S. Government Printing Office, Washington 25, D. C., $0.20.

### THE PHARMACIST AND BETTER HOSPITAL FACILITIES

For community leaders who feel the need for better hospital facilities in their area, but do not know how to go about getting Federal aid, *The Hospital Act and Your Community* will be "must" reading. And the pharmacist's broad interests in medical care should make such community needs of direct concern to him.

As the U. S. Public Health Service pamphlet points out, it is up to each community, in the last analysis, to see that it gets the full benefit of the Hospital Survey and Construction Act. Here is finally offered a comprehensive and well thought out endeavor for construction of hospitals and health facilities—where they are most needed. Federal aid is authorized to the states and communities that are willing to bear their share of the costs and planning. What the Hospital Act means to you

and your community and state is explained clearly in the pamphlet.

THE HOSPITAL ACT AND YOUR COMMUNITY, *U. S. Public Health Service*, Washington 25, D. C.; single copies without charge.

### DRUG AND CHEMICAL ANTIDOTES

An unusually well prepared booklet on antidotes for drugs and chemicals has been compiled and issued by the California State Board of Pharmacy. In this work the Board secured the cooperation of universities in the state and of public toxicologists and public health officials. A table of essential equipment and supplies, an outline of general procedures and specific instructions under individual toxic substances comprise the booklet. L. M. Walsh, Board secretary, indicates that single copies will be made available to non-Californians who have a particular interest in the subject.

CALIFORNIA OFFICIAL ANTIDOTES—*California State Board of Pharmacy*, 515 Van Ness Avenue, San Francisco 2; 30 pp., single copies without charge.

### SUGARS IN PHARMACY

Pharmacists are well aware of the importance of sugars in formulating medication. Not many are apt to have a clear idea of the extent to which sugars are used, and their fascinating history, without a reading of *Sugars and Sugar Derivatives in Pharmacy.*

The fact is that sugar was recognized as a medicine or as an indispensable ingredient of medicines long before it was valued as a food. In the historical portion of his booklet Dr. Pittenger concludes from the evidence that the production of solid sugar and its medicinal use goes back at least to 300 A.D.

The historical account is followed by short discussions of the nature, significance, and uses of the individual sugars. An appendix lists and classifies preparations of the U. S. P., N. F., and Pharmaceutical Recipe Book that contain sugars or sugar derivatives.

This survey of the role that sugars have played and continue to play in the practice of pharmacy is authored by an eminent pharmacist and life member of the A. PH. A., Paul S. Pittenger, now vice-president of Sharp & Dohme, Inc. A. PH. A. members will recall his service to the ASSOCIATION as first vice-president, member of the N. F. Committee and chairman of the Scientific Section.

SUGARS AND SUGAR DERIVATIVES IN PHARMACY—Paul S. Pittenger—*Sugar Research Foundation, Inc.*, 52 Wall St., New York 5; 53 pp., illus., no charge.

# E. H. WIRTH, PHARMACEUTICAL SCIENTIST, DIES

ELMER H. WIRTH, one of the country's leading pharmacognosists and a member of the U. S. P. Revision Committee and the Committee on National Formulary, died on the evening of September 26 at the University of Illinois Research Hospital, Chicago. He was acutely ill for about four weeks, having been stricken immediately after returning from the Milwaukee convention of the A. PH. A. His illness was diagnosed as myocarditis.

Dr. Wirth was born in North Amherst, Ohio, March 11, 1895. He obtained the Ph.C., B.S. and M.S. degrees from the University of Michigan, after which he joined the faculty of the Detroit Institute of Technology as professor of botany and pharmacognosy, and served concurrently as chief chemist for the F. F. Ingram Co. Later Dr. Wirth joined the faculty of the University of Illinois College of Pharmacy.

In 1931, he obtained his doctorate at the University of Leyden in Holland, as Netherlands-American Foundation Fellow under Van Itallie. Upon returning to the United States Dr. Wirth resumed his duties at the University of Illinois, and in 1941 received the rank of professor of pharmacognosy and pharmacology, a post he held until his death.

He was an auxiliary member of the U. S. P. Revision Committee for two decades and since 1940 a member of the Revision Committee. Since 1935 Dr. Wirth had been a member of the Committee on National Formulary. For the past seven years he served as vice-chairman of the Committee and chairman of the Subcommittee on Pharmacognosy. The AMERICAN PHARMACEUTICAL ASSOCIATION, of which Dr. Wirth was a life member, is particularly indebted to him for conscientious service and extensive contributions to development of the drug standardization program of the National Formulary.

Dr. Wirth had also been a leader in the activities of the Plant Science Seminar for many years and its secretary since 1936. His extensive contribution to the science of pharmacy is reflected by many significant papers in the literature.

## TOLERANCES (from p. 545)

pounding by the pharmacists appear more or less accurate. They include all the collected samples, which were to a great extent compounded in the drugstore. The classification of preparations as "extemporaneous" is based largely on the observations of Inspector H. Bernhardt who purchased them, on interviews with pharmacists, and the nature of the preparations. Let us look at some illustrative examples.

### Diluted Hydrochloric Acid

During the past nine years the most consistently bad results have been shown in the preparation of diluted hydrochloric acid, U. S. P. The data obtained, and the extent to which these samples have influenced the composite picture of the precision of drug preparation, are shown in Table V.

The data in Table V show that two main factors influenced the percentage of samples found to be outside the accepted tolerances for all the collected preparations, which include manufacturer's samples as well as extemporaneous samples. Factor 1 is the ratio of the number of extemporaneous samples to the total number of samples. Factor 2 is the ratio of the number of diluted hydrochloric acid samples to the number of extemporaneous samples. Factor 2 loses some of its force in 1945; for, although there is a slight drop in the percentage of bad samples, the small number of diluted hydrochloric acid samples would be expected to cause a greater drop. It so happens that in 1945 the pharmacists proved that there are several other preparations that can keep the percentage of bad samples high.

Why is it so difficult to prepare a 10% solution of hydrochloric acid that will meet the official requirement? This solution is official in the U. S. P. and directions for its preparation are given there. One is directed to take 236 cc. of hydrochloric acid and add water to 1000 cc. A tolerance of ±5% is allowed. The hydrochloric acid directed to be used is a solution containing 35% to 38% of HCl. The specific gravity of a 35% solution of hydrochloric acid is about 1.17, and for a 38% solution it is about 1.19. Using these figures, calculation will show that, depending upon whether the acid solution meets the minimum or maximum U. S. P. requirement, it is theoretically possible, by using the U. S. P. directions, to prepare diluted hydrochloric acid containing in each 100 cc. 9.7 Gm. or 10.7 Gm. of HCl, respectively. We find that the weaker solution is close to the lower limit of 9.5% w/v and that the stronger solution is actually an illegal preparation since it exceeds the higher limit of 10.5% w/v allowed by the U. S. P.

A few years ago we called attention to this fact, and the new U. S. P. XIII directs the use of 234 cc. instead of 236 cc. of hydrochloric acid in the preparation of the diluted acid. This can still yield preparations containing 9.6% w/v and 10.6% w/v of HCl. This change will tend to increase the number of unofficial samples of diluted hydrochloric acid, because even with the older formula the great majority of bad samples were lower than the minimum requirement of 9.5% w/v.

Obviously the tolerance of ±5% for diluted hydrochloric acid is not logical. I recommend that the rubric in the U. S. P. monograph be changed to read as follows: "Diluted Hydrochloric Acid is an aqueous solution containing in each 100 cc., not less than 9 Gm. and not more than 11 Gm. of HCl."

This would not solve the problem with respect to unofficial samples of this solution. In a review of the results obtained with samples of diluted hydrochloric acid purchased in 1943, W. F. Reindollar[10] noted that 47% did not meet the official requirements, and he observed that if the

TABLE V—RELATIONSHIP OF COMPOUNDED PREPARATIONS TO PHARMACEUTICAL ACCURACY

| Year | No. of Total Drug Samples A | % Substandard Samples* | No. of Extempo-raneous Samples B | Ratio of Extemp. Samples to Total Samples $\frac{B}{A}100$ | No. of Dild. HCl Samples C | Ratio of Dild. HCl to Extemp. Samples $\frac{C}{B}100$ | % Dild. HCl Samples Sub-standard | % Total Substand. Samples Due to Dild. HCl |
|---|---|---|---|---|---|---|---|---|
| 1937 | 1523 | 14 | 214 | 14 | 43 | 20 | 33 | 33 |
| 1938 | 1509 | 14 | 211 | 14 | 16 | 8 | 25 | 11 |
| 1939 | 1407 | 7 | 474 | 34 | 7 | 1.5 | 0 | 0 |
| 1940 | 1547 | 14 | 705 | 46 | 97 | 14 | 23 | 19 |
| 1941 | 1453 | 19 | 885 | 61 | 102 | 12 | 45 | 17 |
| 1942 | 1333 | 20 | 1006 | 76 | 160 | 16 | 50 | 27 |
| 1943 | 1274 | 21 | 896 | 70 | 175 | 20 | 47 | 31 |
| 1944 | 1477 | 21 | 971 | 66 | 137 | 14 | 45 | 20 |
| 1945 | 1412 | 19 | 920 | 66 | 50 | 5 | 38 | 7 |

* Samples did not meet official tolerances or a tolerance of ±10%.

tolerance were doubled to ±10% there would still be 31% of the samples outside the 9% to 11% limits. Data show that a tolerance of ±10% would lower the percentage of substandard diluted hydrochloric acid samples for the year 1942 from 50% to 31%, and for 1944 from 45% to 28%. The ±10% tolerance would result in the lowering of the percentages of all substandard samples, as shown in Table V, for the year 1942 from 20% to 18%, and for the years 1943 and 1944 from 21% to 19%.

## Other Preparations

The extemporaneously prepared samples for the year 1945 are given in Table VI. The number of each type of sample and the percentage of substandard samples indicate the influence which that type of sample exerts on the composite percentage of substandard samples for 1945 as shown in Table V.

## Acetic Acid 10%

Apparently pharmacists find it just as difficult to prepare a 10% solution of acetic acid as a 10% solution of hydrochloric acid. Here again they may use U. S. P. acetic acid in the process, and this acid can vary from 36% to 37% of $HC_2H_3O_2$. If the tolerance in this case were changed from ±5% to ±10%, the percentage of substandard samples of acetic acid 10% would drop from 47.3% to 28.1%. I recommend such a change.

## Phenol Ointments 5% and 3% and Salicylic Acid Ointments 7.5%, 3%, and 2.5%

The high percentage of substandard samples of phenol in petrolatum (46.1% are not within a tolerance of ±10%) is typical of preparations containing phenol. A major factor for the poor showing made with preparations requiring crystalline phenol is the hygroscopic nature of the chemical. This factor could be taken care of by purchasing crystalline phenol in smaller, airtight containers, and keeping the bottle in use in a dry place. Another factor is the small volume of the preparation usually prescribed. The fact that the probability for error varies inversely with the amount of substance being weighed or measured cannot be denied. Undoubtedly the forceful warnings concerning the dangers of handling this substance are a factor in the wide variations shown.

Lythgoe[8] found that in 92 samples of 5% phenol solutions, 55% varied by more than ±10%. He also found that at least one in six samples of liquefied phenol was below official strength.

It is bad enough to have pharmacists use understrength liquefied phenol in compounding aqueous solutions, but why must some pharmacists use liquefied phenol in compounding solutions in oil and in compounding ointments with petrolatum?

The results with the salicylic acid ointment (17.5% are not within a tolerance of ±10%) show that much better results can be obtained with more stable and less caustic ingredients.

## Chloroform Spirit

Results obtained with chloroform spirit N.F. indicated that the official limits of tolerance might be too severe or the assay procedure might require alteration. Our study of the problem[11] resulted in the following changes in the N. F. monograph for this preparation:

1. The rubric statement was changed from a weight-to-volume to a volume-to-volume basis.

2. The tolerance was increased from ±4.2% to from −7.5% to +5%.

TABLE VI—EXTEMPORANEOUS PREPARATIONS, 1945

| Preparation | No. of Samples Purchased | No. of Samples Substandard | Percentage of Samples Substandard |
|---|---|---|---|
| Acetic Acid 10% | 57 | 27 | 47.3 |
| Boric Acid Solution N.F. | 66 | 10 | 15.2 |
| Chloroform Spirit N.F. | 14 | 7 | 50.0 |
| Dil. Hydrochlor. Ac. U.S.P. | 50 | 19 | 38.0 |
| Lime Water U.S.P. | 82 | 10 | 12.2 |
| Lugol's Solution U.S.P. | 79 | 10 | 12.7 |
| Phenol Ointment (5%, 3%) | 39 | 18 | 46.1 |
| Potassium Iodide Sol. N.F. | 194 | 55 | 28.3 |
| Potassium Permanganate Sol. (3.5%, 3%, 2.5%, 1%) | 133 | 22 | 16.5 |
| Salicylic Acid Ointment (7.5%, 3%, 2.5%) | 120 | 21 | 17.5 |
| Silver Nitrate Solution 1% | 186 | 33 | 17.7 |

3. The old assay, which gave consistently low results, was dropped in favor of the recommended procedure.

Based on the tolerance official at the time, 7 of the 14 samples of chloroform spirit purchased in 1945, or 50%, failed to meet the requirements. Based on the tolerance now official this is reduced to 2 samples, or 14.3%, outside the limits. We felt that the new tolerance was sufficiently lenient. In 1946, 40 samples of chloroform spirit were purchased, of which 11 samples, or 27.5%, did not meet the old tolerance. Not one of these substandard samples, 10 of which were low and 1 was high, could meet the new toler-

ance either, and only two of them would fall within a tolerance of ±10%. This is not at all heartening.

## Potassium Permanganate Solution

The relatively low percentage (16.5%) of samples of potassium permanganate solutions that did not fall within the set tolerance of ±10% is still not too good. Lythgoe[8] reported results with 17 samples of 5% potassium permanganate solution which showed that 80.8% of the samples did not meet a tolerance of ±10%. It appears that Lythgoe's samples were collected by inspectors unknown to the pharmacists. This procedure would very likely cause some increase in the percentage of substandard samples purchased, but our prescription study of solutions indicates that Maryland pharmacists could be expected to do a better job than Lythgoe revealed by his data.

## Silver Nitrate Solution

The 17.7% of 1% silver nitrate solutions which did not meet a tolerance of ±10% is too high a proportion. Lythgoe found that with 20 samples of 2% silver nitrate solution 40% of them did not meet a tolerance of ±10%.

## Potassium Iodide Solution N. F.

The National Formulary gives directions for preparing this solution. It directs the solution of 100 Gm. of potassium iodide in enough water to make 100 cc. of solution. We usually purchase ½ fl. oz. or 15 cc. of this solution. Weighing 15 Gm. of a very pure and stable salt should be done without much variation. Still we find that 28% of the samples purchased failed to meet the official tolerance of ±3%. This is better than the results noted in 1944 when 148 samples of this solution were purchased and 33% of them failed to meet the specified official tolerance.

## Boric Acid Solution N. F.

The N. F. directions for preparing this solution should yield a 5% solution. A minimum tolerance of −15% is allowed but no maximum tolerance is given. This allows the preparation of a saturated solution of boric acid which may contain about 5.3% of boric acid at 25° C. Taking only those preparations which fail to meet the minimum requirement of 4.25 Gm. per 100 cc., we found 15% of the samples substandard.

A tabulation made by W. F. Reindollar[10] of the boric acid solution samples tested in 1943 shows that 16% failed to meet the official minimum requirement. It also shows that if a tolerance of +10% were set as the maximum, the number of samples containing more than 5.5% of boric acid would raise the substandard samples to 26%.

It might be advisable to set a maximum limit of variation in the case of this solution, because of the tendency of boric acid (even at room temperature) to crystallize from solutions containing more than 5.3 Gm. of boric acid in 100 cc. of solution.

## Lime Water U. S. P.

This preparation consistently shows a relatively small number of substandard samples. The 12% bad samples is the lowest percentage for the extemporaneous preparations in Table V. In 1943, when 134 samples of lime water were tested, only 6% failed to meet the U. S. P. requirement. The minimum requirement for this solution is 0.14 Gm. of $Ca(OH)_2$ in 100 cc. Of the 8 samples classed as unofficial in 1943, three contained over 0.135 Gm. in 100 cc. Counting these as 0.14 Gm., the percentage of bad samples would be 4%. This is getting close to a practically irreducible figure.

## Phenacetin Capsules 5 Grains

A number of 5-gr. phenacetin capsules were purchased at different drugstores during 1945. Since no definite standards exist for this type of preparation, they were not included in Table V. Results of the analyses of these samples are given in Table VII. In addition to variation in total weight, the average of the variations for the individual units in each set of 12 capsules, and the variation of the lightest and heaviest capsules from the theoretical mean, there are listed the number of capsules in each set which exceed tolerances of ±10%, ±15%, and ±20%.

Of the 31 sets of capsules studied, 7 sets (23%) exceeded a tolerance of ±5% for the net weight of the combined capsule contents. In the average unit variation, eight sets (26%) exceeded a tolerance of ±5%; 5 sets (16%) exceeded a tolerance of ±7.5%; and 4 sets (13%) exceeded a tolerance of ±10%. Eleven sets (36%) had one or more capsules which exceeded a tolerance of ±10%; 4 sets (13%) had capsules which exceeded a tolerance of ±15%; and 2 sets (6%) had capsules which exceeded a tolerance of ±20%.

Examination of 25 sets of 5-gr. aspirin capsules showed values very similar to those for phenacetin capsules. Twenty-two sets of 5-gr. quinine capsules showed wider variations, especially in the individual unit variations. Seven sets (32%) had one or more capsules outside a tolerance of ±10%; capsules in 5 sets (32%) were outside a ±15% tolerance; and capsules in 3 sets (14%) were outside a ±20% tolerance.

We must note that the figures for substandard samples given in Table V (second column) include manufacturers' as well as pharmacists' preparations. The advantage of having pharmaceuticals prepared by manufacturing pharmacists who have proper means of controlling and testing their products is emphasized by the fact that a very small percentage of the manufacturers'

TABLE VII—VARIATIONS IN 5-GRAIN PHENACETIN CAPSULES

| SAMPLE NO. | VARIATION IN TOTAL WEIGHT IN % | AVERAGE UNIT VARIATION IN ±% | MAXIMA UNIT VARIATION IN % | | NO. CAPS. OUTSIDE TOLERANCE OF ±10% | NO. CAPS. OUTSIDE TOLERANCE OF ±15% | NO. CAPS. OUTSIDE TOLERANCE OF ±20% |
|---|---|---|---|---|---|---|---|
| 45-217 | −6.5 | 5.4 | −17.2 | +1.2 | 1 | 1 | 0 |
| 45-218 | +1.2 | 1.9 | −1.2 | +4.0 | 0 | 0 | 0 |
| 45-219 | +15.8 | 15.9 | +10.3 | +18.4 | 12 | 8 | 0 |
| 45-220* | −14.0 | 13.8 | −25.4 | −5.6 | 8 | 4 | 3 |
| 45-221 | −1.2 | 2.6 | −7.0 | +3.4 | 0 | 0 | 0 |
| 45-222* | +2.2 | 2.7 | −2.2 | +7.4 | 0 | 0 | 0 |
| 45-223 | −1.8 | 2.2 | −4.6 | +2.0 | 0 | 0 | 0 |
| 45-224 | −5.7 | 6.3 | −11.8 | +3.2 | 2 | 0 | 0 |
| 45-225 | −8.3 | 8.4 | −12.0 | −5.0 | 4 | 0 | 0 |
| 45-226 | −3.0 | 3.4 | −8.6 | +1.6 | 0 | 0 | 0 |
| 45-227 | −1.5 | 3.4 | −7.4 | +6.4 | 0 | 0 | 0 |
| 45-228† | −3.3 | 3.3 | −10.4 | 0.0 | 1 | 0 | 0 |
| 45-229 | +0.2 | 2.7 | −7.4 | +4.4 | 0 | 0 | 0 |
| 45-230 | +1.0 | 1.8 | −1.6 | +4.4 | 0 | 0 | 0 |
| 45-231 | −2.3 | 3.1 | −9.2 | +2.8 | 0 | 0 | 0 |
| 45-232 | −1.7 | 3.1 | −7.0 | +2.8 | 0 | 0 | 0 |
| 45-233 | +9.3 | 10.3 | −5.8 | +13.6 | 8 | 0 | 0 |
| 45-234 | −2.3 | 2.6 | −4.0 | +1.6 | 0 | 0 | 0 |
| 45-235 | +2.5 | 10.7 | −12.0 | +29.6 | 5 | 3 | 1 |
| 45-236 | +1.5 | 2.1 | −5.8 | +1.8 | 0 | 0 | 0 |
| 45-237 | +0.2 | 0.8 | −2.2 | +2.8 | 0 | 0 | 0 |
| 45-238 | +4.2 | 4.6 | −2.4 | +10.0 | 0 | 0 | 0 |
| 45-239 | −2.0 | 2.4 | −5.0 | +0.8 | 0 | 0 | 0 |
| 45-348 | −1.8 | 3.1 | −10.2 | +2.8 | 1 | 0 | 0 |
| 45-349 | −6.2 | 6.6 | −13.0 | +2.4 | 3 | 0 | 0 |
| 45-350 | +1.7 | 1.9 | −0.6 | +5.2 | 0 | 0 | 0 |
| 45-351 | +1.3 | 1.4 | −2.4 | +6.2 | 0 | 0 | 0 |
| 45-352 | +3.5 | 1.9 | 0.0 | +6.0 | 0 | 0 | 0 |
| 45-353 | +2.0 | 4.7 | −12.4 | +9.6 | 1 | 0 | 0 |
| 45-354 | −0.8 | 3.0 | −6.4 | +5.6 | 0 | 0 | 0 |
| 45-355 | −1.0 | 2.2 | −6.4 | +3.2 | 0 | 0 | 0 |

* Eleven capsules in the set. † Six capsules in the set.

samples are found to be unacceptable. Our data for the year 1945 show that 3% of all the manufacturers' samples were substandard, while 28% of the extemporaneous samples were outside the accepted tolerances.

## Discussion

Lythgoe[5] states that the reasons for the wide variations among preparations compounded by pharmacists include "incompetency, inaccuracy, fraudulency, and inattention to business." His studies entitle him to assail the competency and accuracy of some pharmacists. His charge of fraudulency certainly applies to such a small number of cases that it is not only wrong but it is unfair to include it as a reason for inaccurate compounding. His charge of inattention to business undoubtedly applies to the compounding portion of the "drug business," and unfortunately he has grounds for his charge.

Faulty arithmetical conversions also account for many inaccuracies. In spite of this, some pharmacists will insist on making these conversions rather than acquire metric weights and glassware graduated in metric units or rather than use them when they are forced to possess them. The U. S. P. and N. F. are stressing the use of the metric system and the medical schools are teaching the use of the metric system in prescription writing. It is essential that pharmacists should be equipped with the proper tools, especially if they are arithmetically weak.

There is still another reason for compounding inaccuracies, and it is largely psychological. It is a case of the pharmacist knowing too much for his own accuracy. With the great majority of medicinal agents, the accepted dosage is not based on scientifically proved facts. Take our old friend diluted hydrochloric acid. The pharmacist has seen its official average dose change from 1 cc. (U. S. P. X), to 2 cc. (U. S. P. XI), to 4 cc. (U. S. P. XII).

In the case of liquid preparations, the pharmacist knows that no matter how accurately the preparation is made the directions for administra-

tion allow for wide variations in the dosage. Most of these medicinals are administered by the teaspoonful, and the fact that a teaspoonful can vary from 3 cc. to 5 cc. is generally understood. The wide variations in the drops delivered by the many types of medicine droppers, and the influence of viscosity and surface tension on the size of the drop are recognized. With preparations in capsule and powder form, some pharmacists illogically argue that the prepared medicine is not expected to cure in one dose, and that the physiological effects of the active agents are obtained with a number of doses whose average is close to the prescribed unit dose. These reasons for the carelessness in compounding in no way excuse this attitude, which is one of the main causes of inaccurate compounding.

There are some causes for what are reported as substandard samples that are unfairly accredited to inaccurate compounding, and these factors should be taken into consideration in setting the tolerances for different preparations. The more liberal tolerance for chloroform spirit has been cited, and recommendations for a tolerance of ±10% for solutions like 10% hydrochloric and acetic acids have been given.

**The following tolerances, based on the present and other studies, are recommended for prescriptions for capsules and powders:**

**1. The combined determined weights of the prescribed ingredients (weight of the combined unit contents if no other ingredient is added) should not vary more than ±10% from the total prescribed weight.**

**2. The average variation in the weights of the contents of the individual units should not be more than ±10% from the theoretical weight per unit (or from the average unit weight if another ingredient, e.g., lactose, is added), and no single unit should vary more than ±15%.**

**3. The total weight of each prescribed ingredient in the combined contents of all the individual units should not vary more than ±15% from the prescribed weight.**

NOTE: Determinations should be based on the contents of at least ten capsules or powders.

The need for regulatory standards in pharmaceutical compounding is obvious; and the necessity of educating pharmacists to try to comply with reasonable standards is self-evident. It may be argued that any study based on prescriptions obtained by law-enforcement bodies would tend to paint an especially dark picture of pharmaceutical accuracy. Because of limitations of funds and qualified inspectors it is only natural that prescriptions, in many instances, should be taken to drugstores where routine checks have cast suspicion upon the accuracy of their products. But this does not hold for studies of extemporaneous preparations which are purchased at every drugstore in the state.

On the whole, it appears that a greater degree of accuracy is achieved in the compounding of liquid preparations than with other types of medicinal preparations, especially where the dissolved ingredients are stable and easily handled, or are expensive, or toxic, or must be accounted for to some authority as with codeine.

Liberalizing tolerances where this is advisable will not lower the percentage of unacceptable compounded preparations to a satisfactory level. Pharmacy has leaders who strive to raise the standards of pharmaceutical education, and to educate the public to think of pharmacy as a scientific profession. If pharmacy is to have the backing of public health authorities in advancing their professional claim, something should be done to increase the accuracy of pharmaceutical compounding.

## Summary

1. Studies of variations in the compounding of prescriptions and other extemporaneous preparations in drugstores are presented.

2. The various factors which influence accuracy in compounding are discussed.

3. The relative precision with which pharmaceuticals are prepared by drug manufacturers and retail pharmacists is indicated.

4. The influence of certain extemporaneous preparations on the over-all picture of compounding accuracy is shown.

5. Allowable tolerances are discussed and changes in some accepted tolerances are suggested.

6. Tolerances for capsules and powders compounded in the drugstore are offered for consideration.

7. The necessity for increased precision in drugstore compounding is indicated.

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# Science News Capsules

**"H" LACTATION-PROMOTING** factor was described at the Eleventh International Congress of Pure and Applied Chemistry in London by Dr. Mohamed El Shahat of Cairo, Egypt. Small doses of this chemical, obtained from fenugreek oil, were reported to increase the volume of milk from human mothers by 160% to 900% in 158 cases. There was also an increase in the nutritional constituents of the milk.

**THE DEATH RATE** in the U. S. may reach a new low in 1947, according to statisticians of the Metropolitan Life Insurance Co. For the first six months of this year the death rate was 7.6 per 1000 policyholders, which is identical with the previous low in mortality registered in 1942. Tuberculosis deaths are down 8% below the previous minimum, and 35% below the rate ten years ago. In four out of the six months there was not a single death from scarlet fever in the insured group, which includes several million children. The death rate of less than 1.5 per 100,000 for scarlet fever, measles, whooping cough and diphtheria taken together was called "almost incredible but true." The decline in syphilis mortality has amounted to almost 30% in the past ten years, and appendicitis mortality is down more than 70%.

**RADIOACTIVE BACTERIA** and radioactive penicillin have been prepared at the National Institute of Health by introducing radioisotopes into the media upon which the bacteria and the penicillium grow. The radioactive bacteria are being used in studies that may elucidate immune mechanisms. Radiopenicillin is being used to obtain further information on penicillin blood levels and the fate of the drug in the body.

**TEPEXPAN MAN,** the 10,000- to 15,000-year-old fossil skeleton found in Mexico a few months ago, has arrived in this country for study by Mexican and United States scientists at the U. S. National Museum. Tepexpan Man was found at what was once the marshy edge of a lake, where he probably hunted elephants at the time the Ice Age was ending in North America. His bones were found close to the skeleton of an imperial elephant, largest of the ancient mammoths. Although possibly the earliest known North American, Tepexpan Man is relatively "modern," differing particularly from the Neanderthal type by a sharply prominent chin.

**ATOMIC RESEARCH** has advanced far beyond the knowledge from which the atomic bomb was fashioned. One indication of this is a report made to the American Physical Society's Pacific Coast Section. The new 4000-ton cyclotron at the University of California has knocked 22 and possibly as many as 30 particles out of atomic nuclei, transmuted common elements sixteen steps down the periodic table, and opened to study an entirely new series of one hundred or more radioisotopes lighter than stable isotopes.

**SYNHEXYL,** also known as parahexyl, is a new euphoriant that shows promise for treating depression states in the mentally ill. When given orally to 50 patients, the drug produced definite improvement in 36 and no marked side effects were observed. They felt more cheerful, confident and showed more initiative, reports Dr. G. T. Stockings, a Hart Memorial Scholar of the British Medical Association. Dr. Victor Vogel of the U. S. Public Health Service has expressed a less optimistic view, pointing out that the drug produces an acute psychotic excitation in some patients and that the hazards of giving it to unstable patients may outweigh its advantages. Synhexyl was first synthesized in the U. S. by Prof. Roger Adams at the University of Illinois.

**CHLORDANE,** a new insecticide, is said to be about four times as potent as DDT against certain insects. Laboratory tests are reported to show that it is particularly effective against such household pests as roaches, ants, moths and carpet beetles, and against the hordes of grasshoppers that invade Western farm lands. The insecticide is both a stomach and contact poison. Chemically, it is octachloro - 4,7 - methano - tetrahydroindane, which will be marketed in various forms and grades under the trade name Synklor (U. S. Rubber Co.)

**GLYCERIN PRODUCTION** reached an all-time high of 69,000,000 pounds during the first four months of 1947, according to the Glycerin Producers Association. This represents an increase of almost 25% over the same period last year.

**BENZENE HEXACHLORIDE** ("666") may be a sufficiently effective insecticide for flies and mosquitoes so that it will eventually replace DDT and pyrethrum in aerosol bombs, according to U. S. Department of Agriculture entomologists. A drawback of "666" is its persistent disagreeable odor, but it is believed this may be eliminated by improvements in manufacturing processes. Detailed studies of its toxicity to warm-blooded animals also remain to be carried out.

**WORLD'S WORST WORRIERS** appear to be the Aymara Indians, who live on a 14,000-foot-high

plateau in the Andes. Life is hard in the bleak, barren Aymara country, and their hardships seem to be reflected in the mental attitude of the people. Anthropologist Jarru Tschopik, Jr., who has just returned to the U. S. after living in one of their villages for seven years, reports that the Aymaras appear not to like anybody, worry constantly, and practice witchcraft.

**ELECTRO-NARCOSIS** is being evaluated as a much simpler treatment for schizophrenia than insulin shock, which is now the treatment of choice. The technique involves a brief electrical shock, producing convulsions, followed by a weak electrical current passed through the brain to induce a deep, dream-like, seven-minute sleep. In the second group of schizophrenic patients thus treated, Dr. Karl Bowman and Dr. Alexander Simon of the University of California Medical School reported that 5 out of 31 patients recovered.

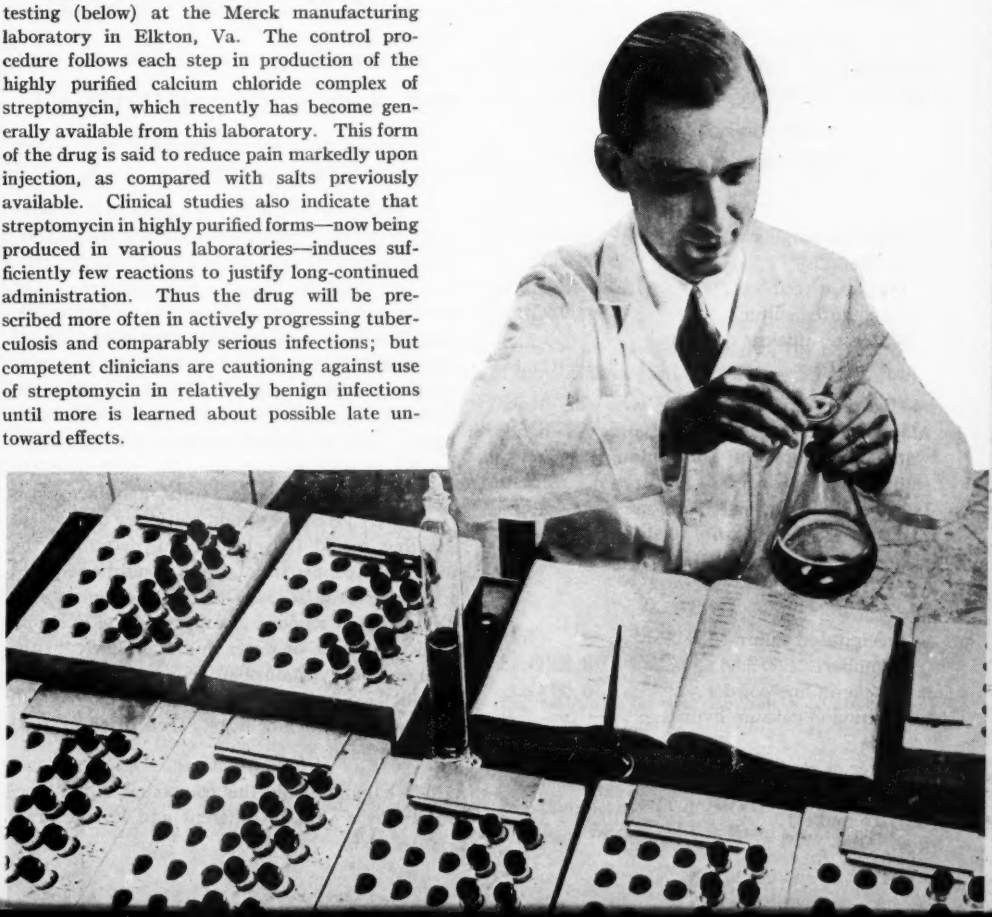
**A MILLION MORE BABIES** were born last year in the U. S. than would have come into the world had the 1933 birth rate continued. The total gain in babies for the country since 1933—over the 1933 birth rate—is four million, according to statisticians of the Metropolitan Life Insurance Co.

**STREPTOMYCIN** samples are prepared for testing (below) at the Merck manufacturing laboratory in Elkton, Va. The control procedure follows each step in production of the highly purified calcium chloride complex of streptomycin, which recently has become generally available from this laboratory. This form of the drug is said to reduce pain markedly upon injection, as compared with salts previously available. Clinical studies also indicate that streptomycin in highly purified forms—now being produced in various laboratories—induces sufficiently few reactions to justify long-continued administration. Thus the drug will be prescribed more often in actively progressing tuberculosis and comparably serious infections; but competent clinicians are cautioning against use of streptomycin in relatively benign infections until more is learned about possible late untoward effects.

**RADAR** has potential value in medicine as an improvement over shortwave diathermy, clinicians at the Mayo Foundation believe. This same type of radiation was under investigation some years before the development of wartime "radar," but was then known as microwave therapy. It has the advantage of a localized beam and permits more rapid cooling of the skin, since the patient is freed from pads.

**WILL IT BE A BOY?** This question may be answered with a fair degree of accuracy for the expectant mother through two new tests developed at the University of Georgia School of Medicine. A blood test is based on the ratio between the "FSH" hormone and "LH" hormone secreted by the pituitary gland. A second test is based on a histologic study of cells shed by the tissues lining the uterus; when these cells fall into definite types, sex of the fetus can be determined with 85.4% accuracy.

**A LIVING MUSEUM** has been found by Smithsonian Institution anthropologists in the small village of Moche on the coast of Peru. Here life goes on much as it did a thousand years ago, with a culture much older than the Spanish Conquest. Moche is touched by the new Pan American highway, and scientists expect to observe here the process of a new culture in rapid development.



# PRESCRIPTION *Information* SERVICE

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## KUMMERFELD'S LOTION

*Kindly advise us of the formula for Kummerfeld's lotion or where it may be obtained.—C. J., New Jersey*

The formulas for this preparation appear in *Pharmaceutical Recipe Book III*, published by the AMERICAN PHARMACEUTICAL ASSOCIATION:

KUMMERFELD'S LOTION

Kummerfeld's Cosmetic Water

I

| | |
|---|---|
| Spirit of camphor | 100 cc. |
| Alcohol | 100 cc. |
| Tragacanth, ribbon | 15 Gm. |
| Precipitated sulfur | 60 Gm. |
| Water, a sufficient quantity, To make | 1000 cc. |

Mix the spirit of camphor with the alcohol. Macerate the tragacanth in 500 cc. of distilled water until thoroughly softened and suspend the sulfur in the product by trituration. Mix the two liquids, and finally add sufficient water to make the product measure 1000 cc.

II

(Hager)

| | |
|---|---|
| Precipitated sulfur | 40 Gm. |
| Camphor | 3.33 Gm. |
| Acacia, in fine powder | 6.66 Gm. |
| Solution of calcium hydroxide | 500 cc. |
| Water or rose water, a sufficient quantity, To make | 1000 cc. |

Triturate the solid ingredients until intimately mixed, using a few drops of alcohol to insure pulverization of the camphor, and incorporate with the solution of calcium hydroxide. Add sufficient rose water to make the product measure 1000 cc.

## PREPARATION OF UNDECYLENATE

*Would you please let me know how to make copper undecylenate?—I. L., Montreal*

Pure undecylenic acid is an unsaturated fatty acid having the formula $CH_3CHCH(CH_2)_7COOH$. The commercial product is seldom strictly pure but, like oleic and stearic acids, a mixture. The most accurate way to make copper undecylenate, therefore, is to determine first the acid value of the undecylenic acid to be used. Then, to a convenient weight of undecylenic acid add about ten times this quantity of water and heat on a water bath. Add, in divided portions, the calculated weight of sodium carbonate to neutralize the acid, and continue heating until saponification is complete. From the weight of sodium undecylenate that would thus be formed, determine the amount of copper sulfate that would be required to convert the sodium salt to the cupric salt. Dissolve that amount of copper sulfate in a convenient volume of water and add slowly to the sodium undecylenate solution. A curd of copper undecylenate will form, which is filtered off, washed well with hot water, then dried at 100° and powdered.

We have prepared this compound in the laboratory by a slightly different and less accurate

method. Assume the undecylenic acid to be chemically pure. The neutralization reaction can then be stoichiometrically written as: $Na_2CO_3 + 2HC_{11}H_{19}O_2 \rightarrow 2NaC_{11}H_{19}O_2 + H_2O + CO_2$. By simple proportion 25 Gm. of undecylenic acid would require about 7.2 Gm. anhydrous sodium carbonate for neutralization. Twenty-five grams of undecylenic acid and 250 cc. of water were heated together and neutralized with 7 Gm. of sodium carbonate; 1 cc. of the resulting solution was added to 5 cc. of water and a drop of phenolphthalein added. The solution remained colorless. Small amounts of sodium carbonate were added with continued heating and stirring until the solution, when tested in this manner with phenolphthalein, gave a very faint pink color.

The amount of copper sulfate ($CuSO_4 \cdot 5H_2O$) required to react with the sodium undecylenate was then calculated, based on the following equation from which the purity of sodium undecylenate is assumed:

$2NaC_{11}H_{19}O_2 + CuSO_4 \cdot 5H_2O \rightarrow Cu(C_{11}H_{19}O_2)_2 + Na_2SO_4 + 5H_2O$.

Again going back to the 25 Gm. sample of undecylenic acid, 16.9 Gm. of $CuSO_4 \cdot 5H_2O$ is required.

The copper salt is filtered, washed and dried as mentioned above.

## INSTRUMENT STERILIZATION

*Will you please submit a formula for cold sterilization of instruments? The physician that requests such a solution has used one in the hospital known as Bard-Parker's solution.—E. K., Missouri*

Bard-Parker's Solution has been widely used for the chemical disinfection of instruments, but there appears to be a tendency to vary the composition depending upon the desires of the user. One of the early formulas is given below:

| | |
|---|---|
| Formaldehyde | 3% |
| Alcohol | 77% |
| Acetone | 10% |
| Inert ingredients (mostly water) | 10% |

A more recent formula is said to be as follows:

| | |
|---|---|
| Isopropyl alcohol | 48.12% |
| Methyl alcohol | 3.08% |
| Formaldehyde | 8.00% |
| 3,9 - Diethyltridecanol - 6 sodium sulfate | 0.187% |
| Inactive ingredients (water, etc.) | 40.62% |

This later solution is apparently more effective due to addition of the wetting agent.

## TRIMETHADIONE

*Can you supply the name of the manufacturer of the chemical trimethadione, used in treating epilepsy?—E. B., West Virginia*

Trimethadione is the name assigned an anticonvulsant drug which chemically is 3,5,5-trimethyloxazolidine-2,3-dione. This product is manufactured and distributed exclusively by Abbott Laboratories, North Chicago, Ill., in the form of capsules and in a flavored aqueous solution. Their copyright name for the drug is Tridione.

## FORMULA FOR HAND CREAM

*Do you have a formula for a hand cream for dry skin, perhaps one containing wool fat?—H. M., Colorado*

The following formula taken from the *Pharmaceutical Recipe Book III*, a publication of this ASSOCIATION, should fill your need:

| | |
|---|---|
| White wax | 114 Gm. |
| Spermaceti | 85 Gm. |
| Hydrous wool fat | 156 Gm. |
| Expressed oil of almond or persic oil | 463.5 Gm. |
| Rose water | 175 cc. |
| Sodium borate | 2.5 Gm. |
| Antioxidant, if desired | |
| Perfume, as desired | |
| To make about | 1000 Gm. |

Melt the white wax and spermaceti (with the antioxidant) on a water bath, add the expressed oil of almond and warm to 70° C. Dissolve the sodium borate in the rose water and bring to the same temperature as the melted mixture, to which it is added gradually with constant stirring. Pour into a slightly warmed mortar containing the wool fat and stir. Add the perfume and stir until cold.

The hydrous wool fat may be replaced by theobroma oil, if desired.

## A STABILITY PROBLEM

*I am interested in compounding a solution of sodium sulfadiazine with sodium bicarbonate suitable for internal use for adults but chiefly for children. Physicians in my city are prescribing sulfadiazine in a thick preparation. If both the dispenser and the patient do not thoroughly*

*shake this type of preparation the sulfadiazine will settle out and when the latter doses are taken the patient, especially a child, could suffer toxic effects.—B. D., Connecticut*

It is generally conceded that solutions of sodium sulfadiazine are less stable than sulfadiazine itself. The following preparation, developed by Chiba and Phillips (*Bull. Amer. Soc. Hosp. Pharm.*, 3 : 22, 1946), we believe would be suitable for your purpose. This contains sulfadiazine powder suspended in an aqueous solvent, but it also contains a relatively large amount of sodium citrate that would have an alkalizing effect on the urine similar to sodium bicarbonate.

| | | |
|---|---|---|
| Sulfadiazine powder | 62.5 | Gm. |
| Pectin | 7 | Gm. |
| Sodium citrate | 75 | Gm. |
| Benzaldehyde | 0.2 | cc. |
| Zephiran chloride solution, 12.5% | 1 | cc. |
| Syrup | 500 | cc. |
| Orange flower water | 200 | cc |
| Distilled water, *q. s.* | 1000 | cc. |

Rub the pectin with a small amoun of the syrup; add remainder of the syrup and then add remainder of the ingredients, having dissolved the sodium citrate in the orange flower water. Mix well and pass through a homogenizer.

## NOMINATIONS FOR IODINE RESEARCH AWARD OPEN UNTIL JANUARY 1

NOMINATIONS are now being received by the AMERICAN PHARMACEUTICAL ASSOCIATION for the Iodine Educational Bureau Award recognizing outstanding research in the chemistry and pharmacy of iodine and its compounds as applied in pharmacy or medicine. Any member of the ASSOCIATION may propose a nominee by submitting specific identification of the work to be considered in the competition, a biographical sketch of the nominee including date of birth, and a list of his publications. Eight copies of the nomination must be submitted to the Secretary of the AMERICAN PHARMACEUTICAL ASSOCIATION, Dr. Robert P. Fischelis, 2215 Constitution Ave., N. W., Washington 7, D. C. To be eligible for the 1948 award, nominations must be received before January 1.

Establishment of the new iodine award was announced at the Milwaukee convention of the AMERICAN PHARMACEUTICAL ASSOCIATION, which will administer the competition.

A nominee must be a resident of the United States or Canada. He must have accomplished outstanding research in the chemistry or pharmacy of iodine and its compounds as applied in pharmacy or medicine, including diagnostic use.

During the period covered by the nomination the nominee shall have been actively engaged in, shall have completed, or shall have published a report upon the line of investigation for which the award is made. During the two years prior to nomination, a nominee shall not have been engaged in research under sponsorship of the Iodine Educational Bureau, Inc.

The award consists of $1000 and a diploma setting forth the reasons for selection of the recipient. It may be presented biennially at the annual meeting of the ASSOCIATION.

The recipient will deliver a paper or lecture upon the subject of his scientific work at the meeting at which the award is conferred. His paper, or address, will then be published in the JOURNAL of the ASSOCIATION. In addition to the sum of the award, the recipient will receive an allowance of not more than $250 to defray expenses of attending the meeting.

The recipient will be selected by an award committee, which is appointed by the chairman of the ASSOCIATION'S Council and which functions under prescribed rules. Should the award committee fail to find a suitable recipient in any biennium, two awards may be made during the next biennium in the same or successive years, if suitable recipients are selected.

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*Feinberg and Bernstein, J.A.M.A. 134: 874 (July 5) 1947

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PHARMACEUTICAL PRODUCTS, Inc., SUMMIT, NEW JERSEY

# A SUSPENSION OF PARALDEHYDE

by CARL C. PFEIFFER and HARRY L. WILLIAMS

DEPARTMENT OF PHARMACOLOGY, UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE, CHICAGO 12

**GUM TRAGACANTH AND GLYCYRRHIZA SYRUP OFFER A MORE PALATABLE PREPARATION OF HYPNOTIC KNOWN FOR UNPLEASANT TASTE AND ODOR**

ALTHOUGH paraldehyde is an effective hypnotic drug its unpleasant taste and odor make intragastric instillation, via a stomach tube, almost the only acceptable route of administration. Most confusing to the critical observer are the directions in books of pharmacology[1] and therapeutics[2] which advise giving paraldehyde on chipped ice. Since the drug congeals at 11° C.[3] almost the entire dose remains as a coating on the ice chips when the diluting water or milk is added. The solubility of the liquid is one part in eight parts of water at 25° C., but the rate of solution of the congealed material in ice water is apparently very slow. The reliability and extremely low toxicity of oral paraldehyde would well justify the time and effort spent in preparing more palatable preparations.

## Experimental

A suitable suspension of paraldehyde in water may be made by the use of powdered gum tragacanth. Such suspensions can be made to contain as high as 50% (by volume) of paraldehyde and are stable over a period of at least one year when stored in brown bottles at room temperature.

Dilution of the suspension with tap water or ice water (as at the time of administration) does not result in any detectable separation of the suspended medicament. When two or three teaspoonfuls of the suspension are diluted in a glass or one-half glass of water, the effect on the mucous membranes of the mouth and oro-pharynx is strikingly similar to that of menthol, namely, a mixed sensation of mild heat and coldness. This suspension has been tested on patients in the Illinois Neuropsychiatric Hospital and has been found quite palatable.

Powdered gum acacia will not, under these same conditions, suspend paraldehyde.

## Preparation

To 200 cc. of paraldehyde in an electrically operated blender* 10 Gm. of powdered gum tragacanth is slowly added while the motor is run either at slow speed or intermittently (to prevent splashing). When the tragacanth is thoroughly suspended, 300 cc. of water is added rapidly while the blender is operating at high speed. When all of the paraldehyde is suspended and no traces of oily liquid remain on top of the suspension, the process is complete.

At this point glycyrrhiza fluidextract or anise oil may be added as a flavoring agent. Cinnamon and peppermint oil are also effective flavoring agents but they tend slightly to break the suspension.

Since the demulcent action of glycyrrhiza masks the taste most successfully, an alternate and apparently equally satisfactory method of preparing the suspension is to use 300 cc. of glycyrrhiza syrup instead of the water in the second step of the process. When the syrup is used the amount of tragacanth can be reduced to as low as 1.5% since the emulsifying action of the glycyrrhiza apparently substitutes to some extent. On long standing, however, this separates into two layers and a "shake label" is needed.

This could be prescribed as follows:

| ℞ | Gm. or cc. |
|---|---|
| Paraldehyde USP..... | 50 |
| Pwd. gum tragacanth..... | 2 |
| Glycyrrhiza syrup, *q.s.ad*..... | 120 |

Make a suspension.

Label: Shake before using. One teaspoonful in ice water as needed for insomnia.

When the preparation is stained with the fat-soluble dye, Sudan III, and examined under the microscope some of the globules of paraldehyde take this fat-soluble stain. The suspended red globules apparently indicate an emulsion or suspension of paraldehyde in water.

* Waring-Type Blender.

The use of an homogenizer to further subdivide the suspension was unsuccessful, in that the suspension was partially separated by this process.

Since this suspension contains about 40% paraldehyde, 5 cc. or one teaspoonful will provide the 2 cc. U. S. P. dose of paraldehyde.

We have had no experience as yet with rectal administration of the suspension but it is believed that retention of this preparation should be better and the pathological effect on the mucous membrane decreased from that produced by undiluted paraldehyde.

Other diluted preparations of paraldehyde available are an elixir of paraldehyde, R. B. III,[4] which contains 24% paraldehyde, 50% alcohol and approximately 25% glycerin, and a mixture of paraldehyde, R. B. II.[5] While these preparations are probably palatable if well diluted, the high concentration of organic solvents in the former is not desirable in the treatment of alcoholics and epileptic patients, and the mixture of paraldehyde is much too dilute for use in adults.

## Summary

Paraldehyde may be suspended in water by the use of 2% of powdered gum tragacanth. Glycyrrhiza syrup is the best masking agent for the menthol-like taste of this suspension, which is more palatable than paraldehyde diluted with ice water. With a 40% suspension the U. S. P. dose of paraldehyde (2 cc.) is contained in one teaspoonful (5 cc.).

### REFERENCES

1. Goodman and Gilman, "The Pharmacological Basis of Therapeutics," Macmillan, New York, 1941, p. 179.
2. Beckman, "Treatment in General Practice," ed. 3, Saunders, Philadelphia, 1940, p. 608.
3. "U. S. Pharmacopœia XIII," Mack Printing Co., Easton, Pa., 1947, p. 378.
4. "The Pharmaceutical Recipe Book," ed. 3, AMERICAN PHARMACEUTICAL ASSOCIATION, 1943, p. 33.
5. "The Pharmaceutical Recipe Book," ed. 2, AMERICAN PHARMACEUTICAL ASSOCIATION, 1936, p. 121.

# CINCHONA REGULATIONS FURTHER MODIFIED

REMAINING government controls over cinchona and its alkaloids are further modified by amendment to order M-131, issued by the Office of Materials Distribution on September 12. The effects of the revised regulations, as they apply to the practicing pharmacist, are outlined below:

1. *QUINIDINE.*—Controls over acquisition and dispensing by the practicing pharmacist remain the same *except* that to obtain quinidine from a supplier it is no longer necessary to submit a certification for each order. Although the certificate is not required the following restrictions remain fully in force: (*a*) No more than two ounces of quinidine or its salts may be obtained during any calendar month without special authorization. (*b*) At no time may a pharmacist accept delivery of more quinidine than will give him a total stock of four ounces (or its equivalent in standard dosage forms). (*c*) Quinidine may be dispensed only upon new prescriptions for not more than 50 three-grain capsules or tablets (or the equivalent of 150 grains in other dosage form). (*d*) The physician must indicate on the prescription that it is intended for cardiac disorders or is prescribed pursuant to order M-131.

Present restrictions apply only to cinchona bark, quinine and quinidine originating from government stocks and not to privately imported supplies. Because of the nature of remaining restrictions, the source will not ordinarily be in doubt except possibly in the case of quinidine. According to the regulations, pharmacists "obtaining quinidine thought to be privately imported should satisfy themselves, in some reasonable manner, that it was not acquired directly or indirectly from any U. S. Government agency.

"For this purpose, they may rely upon statements in package labelings or upon other written statements from suppliers regarding the source of the quinidine, unless they know or have reason to believe the statements are not true. In general, private imports of quinidine were not resumed until after July 15, 1947. Therefore, quinidine obtained or packaged before that date is likely to have been acquired from government stocks."

2. *QUININE.*—All restrictions on quinine at the level of the retail pharmacy have been removed, both with regard to monthly deliveries and dispensing. Manufacturing pharmacists and others may accept delivery of quinine from the RFC stockpile only as authorized by the Office of Materials Distribution.

3. *TOTAQUINE, CINCHONINE AND CINCHONIDINE.*—All controls over these cinchona derivatives were lifted in November, 1946.

**CONTRACEPTIVE CAPSULES AND SUPPOSITORIES** (See New and Nonofficial Remedies, 1946, p. 359).

The following article now stands accepted:

EATON LABORATORIES, NORWICH, N. Y.

**Lorophyn Vaginal Suppositories:** Suppositories consist of a low melting mass prepared from the formula:

| | |
|---|---|
| Phenylmercuric acetate | 0.05% |
| Glyceryl mono-laurate | 10.00% |
| Tween 61 (Sorbitan monostearate-hydroxy polyoxyethylene ether) | 89.95% |

*Actions and Uses.*—See article Contraceptive Capsules and Suppositories.

*Dosage.*—One suppository containing 2.85 Gm.

**ESTROGENIC SUBSTANCES** (See New and Nonofficial Remedies, 1946, p. 443).

The following dosage forms have been accepted:

ENDO PRODUCTS, INC., RICHMOND HILL, N. Y.

**Tablets Estromone:** 1000 international units, 2000 international units and 4000 international units.

**Solution Estromone (in Oil):** 1-cc. ampuls and 10-cc. and 25-cc. vials. Each cubic centimeter contains 2000 international units, 5000 international units, 10,000 international units or 20,000 international units of estrogenic substances in sesame oil. The 10-cc. and 25-cc. vials contain 0.5 per cent chlorobutanol as preservative.

U. S. trademark 345,724.

**THIAMINE HYDROCHLORIDE** (See New and Nonofficial Remedies, 1946, p. 618).

The following dosage forms have been accepted:

E. S. MILLER LABORATORIES, INC., LOS ANGELES

**Solution Thiamine Hydrochloride 10 mg. per cc.:** 1-cc. ampuls.

**Solution Thiamine Hydrochloride 50 mg. per cc.:** 1-cc. ampuls.

**BACTERIAL VACCINE MADE FROM PLAGUE BACILLI** (See New and Nonofficial Remedies, 1946, p. 577).

The following dosage form has been accepted:

CUTTER LABORATORIES, BERKELEY, CALIF.

**Plague Vaccine:** 20-cc. vials containing 2000 million killed bacilli.

## COUNCIL REPORTS

*The Council authorized the publication of a report [J. A. M. A., 133: 693, 1947, and This Journal, 8: 226, 1947] advising against the clinical use of sodium tetrathionate because of the potential dangers of nephrotoxic actions as revealed in animals. Dr. Frank V. Theis takes exception to this caution, believing that there is no danger with clinical doses. Dr. Geza de Takats also has protested against the report. The Council believes that these letters should be published. They are reproduced here.*—AUSTIN SMITH, M.D., *Secretary.*

### SUPPLEMENTAL REPORT ON SODIUM TETRATHIONATE

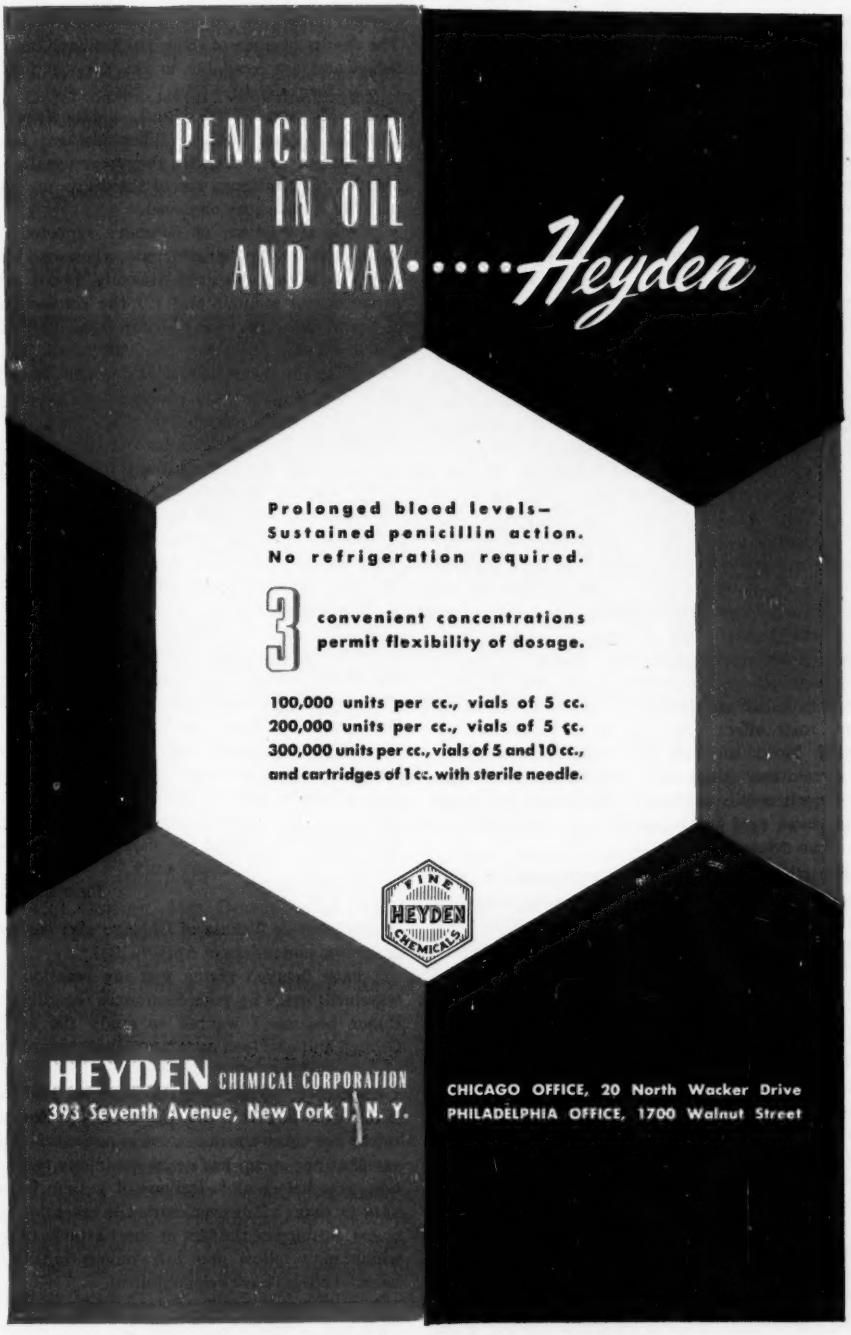
Dr. Austin Smith, Secretary
Council on Pharmacy and Chemistry
535 N. Dearborn Street
Chicago 10, Illinois

Dear Doctor Smith:

I am concerned by the action of your committee in officially advising, in the March 8 issue of the Journal, that the "use of Tetrathionate in medicine should be abandoned" because of its nephrotoxic effect. To abandon the use of Tetrathionate, on the "substantial evidence" you present, would deprive many patients suffering with thromboangiitis obliterans, thrombophlebitis and other related diseases of intravascular clotting from what are believed to be the benefits of its use. Your conclusion is based on the results of a limited study with relatively large doses of the drug given experimental animals. It overlooks completely the clinical investigations and successful use of Tetrathionate as a therapeutic agent. I know of no report of toxic effect from the clinical use of Tetrathionate.

In 1936 Freeland and I were responsible for having Tetrathionate (Searle) prepared and made commercially available. I have used or supervised the use of more than 15,000 ampuls of Tetrathionate supplied to me by G. D. Searle and Company and have been satisfied with the results in treating more than 500 patients. Confirming our observations de Takats (*Surgery*, 14:661 [Nov]. 1943) stated that the "inexpensive and nontoxic sodium tetrathionate is now in routine use on our (his) surgical service" and that "clinically there can be no doubt about the beneficial influence of intravenous sulfur compounds especially in migrating phlebitis"; and "in the acute stages of Buerger's disease the intravenous use of sulfur has given surprising results." Allen, Barker and Hines in their recent book state that to their knowledge "no untoward reactions have followed the administration of sodium tetrathionate." It may be that the Council carrying the weight and responsibility that it does to the medical profession will wish to review its opinion in the light of further evidence on the clinical investigations with sodium tetrathionate as well as interpret the results of animal studies with the therapeutic doses used in clinical medicine. These doses have not been toxic.

The nephrotoxic effects of Tetrathionate which are cited followed the administration of relatively huge doses to experimental animals. For the dog, Chen, Rose and Clows reported the lethal dose as being 1.0 Gm. per kilogram body weight or 140 times the therapeutic clinical dose, while Gilman determined the dose to be 250 mg. per kilogram or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36 times the clinical dose. Gilman's statement that "Tetrathionate is toxic to the renal tubule to a degree that moderate doses produce complete anuria within less than an hour " may be questioned from the data he presented The "moderate doses" he used were excessively large (i.e., 11.0 Gm. in a single injection to a dog produced anuria in seventy-five minutes) and were toxic doses compared to our recommended clinical dose of 0.4 or 0.6 Gm. for an adult weighing over 70 kilograms. His report showed that with 7 times the human dose given rabbits and 16 times the human dose given dogs none of the animals died and there were no demonstrable toxic or ill effects. There are few systemic therapeutic drugs of value which have a greater factor of safety than Tetrathionate.

Prior to our clinical use and investigations of Tetrathionate, we too studied the toxic effects on rabbits. Series of rabbits were given daily intravenous doses of 0.1, 0.2, 0.4 and 0.6 Gm. of Tetrathionate, which were equivalent to 9, 18, 36 and 72 times, respectively, the clinical dose per kilogram recommended for therapeutic use. Daily injections of 0.4 Gm. (35 times the clinical dose) for three days (total of 1.2 Gm.) resulted in death of the animals from twelve hours to three days after the third dose. Autopsy study revealed edema and necrosis of the liver, kidney, heart and other organs. Rabbits given the 0.1-Gm. dose (9 times the clinical dose) daily for twelve days (total of 1.2 Gm.) showed no ill effects, thrived and gained weight. Autopsy study revealed no evidence of nephrotoxic or any other toxic effect. Studies on these animals included blood and platelet counts, hemoglobin, blood clotting time and glutathione, fibrinogen and prothrombin contents. Even with the fairly large doses used in the latter series of rabbits we found no deleterious effect.

The clinical dose which we recommended after extensive clinical and animal investigations with various size doses is 0.4 or 0.6 Gm. of sodium tetrathionate. This is equivalent to an average of 7 mg. per kilogram, a really small fraction of the toxic doses used in the investigations by Gilman. Even our most intensively treated patients show no evidence of nephrotoxic or other toxic effects; some of these have been followed for ten years and have received more than 300 injections. Occasionally, transient reactions with faintness, nausea, abdominal discomfort or weakness have followed an initial or too rapid injection. However, the same reactions occur with the use of sodium thiosulfate. Prompt relief is obtained by the ingestion of milk, food or water. Smaller subsequent doses or slower injection will almost always prevent recurrences of these reactions.

Our clinical investigation during the past ten years has included laboratory studies on the urine, blood cell counts, clotting time, sedimentation rate, basal metabolism rate and determination of the blood cholesterol, lipids, fatty acids, phospholipids, nonprotein nitrogen, urea, protein, creatinine, glutathione, sugar, calcium, potassium, sodium, prothrombin and oxygen and carbon dioxide capacity and content (saturation) of the arterial and venous blood. The results of some of these studies have been published and are available in the surgical literature (*Arch. Surg.*, 38:191 [Feb.] 1939; 40:190 [Feb.] 1940; *Surgery*, 11:101 [Jan.], 1942; *Ann. Surg.*, 113:1107 [June], 1941). When changes followed injections of Tetrathionate they were usually favorable for the continued use of the drug; no deleterious effects have been observed.

My own analysis of Gilman's reported observations is that (1) Tetrathionate, when used in doses comparable to those used clinically, is not toxic to experimental animals and (2) the conversion and elimination of the Tetrathionate from the body are much slower than for the thiosulfate solution. However, the delay in eliminating the drug in the body is not sufficiently prolonged to produce deleterious or toxic cumulative effect from daily injections and is the reason for our original decision, ten years ago, for substituting the tetrathionate for the thiosulfate solution. We arrived at the same conclusion from the results of studies on the elimination of the sulfur in the urine. This part of the investigation was done with the cooperation of Dr. Andrew McNally, toxicologist, who originally suggested the use of Tetrathionate.

In view of the benefit which so many patients with thromboangiitis obliterans, thrombophlebitis and other diseases with tendency for intravascular clotting have received from the therapeutic use of Tetrathionate (Searle) and in the absence of any clinical or laboratory evidence of toxicity in the doses we advise, it would appear that the Council should review all the information available and reconsider its recommendation that the "use of Tetrathionate in medicine should be abandoned."

Yours truly,

FRANK V. THEIS

Dr. Geza de Takats of Chicago also has written as follows under date of April 7, 1947:

I have delayed giving you my reaction to the statement made by your committee regarding tetrathione because I wanted to study the article of Gilman and also look over our records regarding any untoward results with the drug.

Obviously, sodium tetrathionate as used in Gilman's experiments was being used in a dose about thirty-five times the dose used in patients. I might say that our group has never made any renal function tests before and after use of sodium tetrathionate in man. However, with the exception of dizziness, flushing of the face or short attacks of nausea which may follow any intravenous injection, no harmful effects have been obtained.

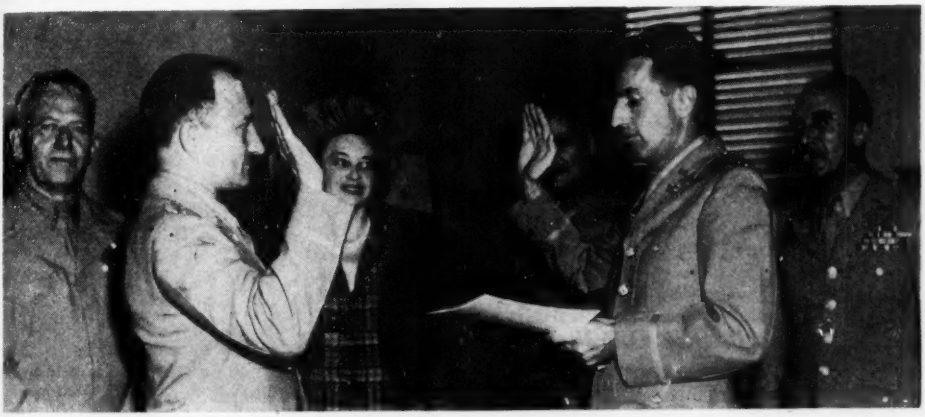
My assistants and I use tetrathione rather sparingly and certainly have made no such extensive use of it as has Dr. Frank Theis and his group. However, if your committee based its opinion on the data available from Gilman's experiments, very few potent drugs can be used at present.

If you gave a dog or rabbit thirty-five times the dose of prostigmine, mecholyl, heparin, dicumarol and many others, there would be widespread toxic damage and mortality among the animals.

Certainly the quoted experiments do not reproduce clinical conditions and I am writing to suggest that the committee review its statement and if necessary conduct some more experiments based on controlled clinical material.

No nephrotoxic effects were observed in the patients treated by Dr. Theis and his associates and apparently these investigators feel that there is little if any danger of such effects from the doses that they have used clinically. However, when an agent is capable of interfering with the important but insufficiently known SH functions, a word of caution is not amiss. It should be realized at least that the dosage must be kept at a minimum and the renal function kept under close observation. Further observations may reveal valuable data.

# PHARMACIST BECOMES CHIEF OF NEW CORPS



COL. OTHMAR F. GORIUP, pharmacist and member of the AMERICAN PHARMACEUTICAL ASSOCIATION, is shown above being sworn in as chief of the new Medical Service Corps of the Army on September 29. Left to right are Maj. Gen. Malcolm C. Grow, the Air Surgeon; Col. Goriup; Mrs. Goriup; Col. Paul I. Robinson, MC, chief of the Personnel Division, Surgeon General's Office; Lt. Col. R. J. O'Connor and Brig. Gen. George E. Armstrong, Acting Surgeon General.

Col. Goriup was formerly chief of the Allotment and Procurement Branch of the Medical Personnel Division in the Office of the Air Surgeon. He is the first chief of the new Corps, established by the last Congress, which will include commissioned specialists in many fields allied to medicine, such as bacteriologists, pharmacists, psychologists, sanitary engineers, optometrists, chemists and electronics experts. Another pharmacist will be appointed to serve under Col. Goriup as head of the Pharmacy, Supply and Administration Section.

In referring to the qualifications Col. Goriup has for the new Medical Service Corps post, Gen. Armstrong cited the distinguished record Col. Goriup made during the war in the Air Transport Command. Last March he was awarded the Legion of Merit for his exceptional services in assisting in the development of the program for air evacuation of the wounded and for improvement of the ATC medical service.

Since August, 1946, Col. Goriup has been chief of the Allotment and Procurement Branch in the Office of the Air Surgeon. From June, 1942, until October, 1945, he was chief, Supply and Operations Division and Administrative Assistant in the Office of the Surgeon, Headquarters, Army Transport Command, Washington, D. C. From March, 1941, to June, 1942, he was Administrative Officer at the Station Hospital at Langley Field, Va.

Col. Goriup, who is forty-two years old, was graduated from the University of Pittsburgh in 1929 with a Graduate Pharmacist degree and from St. Bonaventure in 1939 with a Bachelor of Science degree. He is a member of the AMERICAN PHARMACEUTICAL ASSOCIATION, American Chemical Society, American Society of Hospital Pharmacists, Kappa Psi pharmaceutical fraternity, and a fellow of the American College of Apothecaries.

Col. and Mrs. Goriup and their son, Franklin, live in Fairlington, Va.

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# Typical Days

FROM THE SECRETARY'S DIARY FOR SEPTEMBER

—1st—

ENROUTE from Milwaukee, where the 1947 convention is now history, to Philadelphia to pay our last respects to Mrs. Ambrose Hunsberger, who passed away while on vacation in Maine. A perfect lady, gone to her eternal reward, mourned by hundreds of friends who knew her as "first lady" when her husband was president of the N. A. R. D., the Pennsylvania Pharmaceutical Association and numerous other pharmaceutical organizations in Philadelphia and who graced many a convention of the A. PH. A. Our sympathies go out to Ambrose Hunsberger, pioneer exclusive prescription pharmacist in Philadelphia, vice-president of the Philadelphia College of Pharmacy and a preceptor par excellence as this pharmacist can testify from personal experience under his tutelage.

As our train wends its way over the Pennsylvania mountains and 'round the horseshoe bend there is plenty of time to gaze at the beauties of nature and to let the mind wander back to the happenings of the previous week and to the anticipated progress that lies in the future. We have a feeling of pride in the achievements of the members and officers of the A. PH. A., which continue to bring us increased respect from the various branches of the government, the organized sister professions and the many workers in our own ranks who have occasion to make use of the facilities of the ASSOCIATION and to test its ability to serve American pharmacy. Team work is the order of the day.

—2nd—

Putting Labor Day behind us so early in September seems to provide a running start for the busy fall and post-convention season. On the return to the office many problems await solution, but we have gathered renewed confidence in the future of this organization from the many pleasant contacts at Milwaukee.

It is particularly pleasing to note the splendid progress being made on the memorial flagstaff and surrounding marble bench. Much accumulated mail to peruse and many a report and document await reading and disposal.

—3rd—

A pleasant chat with Carson Frailey, discussing among other things the pending Pharmaceutical Survey reports as they relate to prescription practice. Now reviewing advertising and publication problems with Messrs. Nowell, Winter and Powers, while Glenn Sonnedecker is putting the heat on the printers at Easton to bring the convention issue of the JOURNAL to our readers on time.

—4th—

Saddened by word from Dean Schaefer that Emeritus Dean Anderson of the Brooklyn College of Pharmacy passed away. Among the visitors today were numbered Al Skean of the Atlantic City Convention Bureau who seems happy over the prospect that A. PH. A. *may* meet in Atlantic City, in 1950.

—5th—

Working on post-convention business including minutes of the "old" Council meetings prior to departure for a week end in New Jersey.

—6th—

Paying final tribute to William C. Anderson, past honorary president of the A. PH. A. and former dean of the Brooklyn College of Pharmacy, who was buried from his boyhood home in Keyport, N. J. Here met a large delegation of New York pharmacists including Hugh Craig, Bob Gerstner, Sasmor, Fonda, Heimerzheim, Christ and many others. After the services, with Treasurer and Mrs. Hugo Schaefer to spend a quiet afternoon transacting A. PH. A. fiscal business and reviewing the resolutions.

—8th—

For the first time in several weeks the entire staff was again assembled and there was much discussion of the work ahead as outlined for us at Milwaukee. In the late afternoon a visit with Congressman Durham who has agreed to accept the honorary chairmanship for the dedication ceremonies incident to erection of the war memorial.

—9th—

Now off to Baltimore to inspect some printing plants and to visit with H. A. B. Dunning whose advice on A. PH. A. problems is always sound and forward-looking. Returning in time to Washington to complete the work on the bulletin which carries information on resolutions passed at Milwaukee.

—10th—

Rushing through the mail and office routine in order to leave with Dr. Powers on the noon train for Trenton, N. J., and from there via automobile to Pocono Manor for the three-day meeting of the U. S. P. Revision Committee. This is an ideal spot at which to combine some recreation with the intricate discussions of U. S. P. revision problems in subcommittees as well as meeting with the Committee as a whole.

—11th—

All day at the Pocono Manor Inn sitting first with the general Committee of Revision where the question of including information on therapeutics in the U. S. P. again occupied a goodly portion of the Committee's time without reaching any new conclusions.

After the luncheon the Committee split up into subcommittees with most interesting discussions of problems of scope, galenicals, chemicals and packaging. The discussions continued after dinner

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but there were also opportunities for visits with friends of long standing and the discussion of extra-pharmacopœial matters.

—12th—

All day the meetings of subcommittees continued, and it is remarkable to what an extent decisions can be reached promptly when personal contact replaces lengthy correspondence.

—13th—

And now the final session of the full Committee of Revision, followed by the return trip to Washington via New York where President Zugich, Secretary Godley and Treasurer Sister Etheldreda of the American Society of Hospital Pharmacists met with Gloria Niemeyer and the Secretary of the A. PH. A. to discuss procedures for further integration of the activities of the Society and the A. PH. A. in the year ahead.

—14th and 15th—

After a Sunday spent in peace at the office, the mid-September rush of activity at the headquarters was on in full force on Monday morning. Among the visitors were Prof. Liberalli of São Paulo University, School of Pharmacy in Brazil, and Deputy Surgeon General Armstrong of the U. S. Army who inspected the building and facilities of the ASSOCIATION and seemed much pleased with future possibilities for cooperation in the development of the Medical Service Corps.

—16th—

At lunch with Comdr. Briggs of the Veterans Administration, discussing many angles of the pharmacy service so ably administered by him. An indication of the interest of railroads in recovering their lagging passenger traffic was a visit from a representative of one of the leading roads, and we told him plenty about the service we were not getting. After office hours a futile trip around Washington with a real estate agent who did not have the keys to places that looked good.

—17th—

This afternoon a pleasant visit with Adm. Pugh, Deputy Surgeon General of the Navy, discussing problems connected with the organization of the Medical Service Corps in the Navy and particularly the Pharmacy Section. Now marveling at the precision of the stonecutters who fashioned the marble bench which will surround the memorial flagstaff on our grounds. A beautiful piece of sculpturing enhanced by the setting in which it will find permanent rest.

—18th—

The day's proceedings enlivened by a telephone call from Troy Daniels in far off San Francisco urging an early visit to settle preliminary convention plans for 1948. In the afternoon to the Federal Security Agency to meet the new administrator, Oscar Ewing, who impresses one as a capable official with sound and constructive plans for the future of the Public Health Service, the Food and Drug Administration, the Social Security Board and the Office of Education, all of which come under his jurisdiction. Without question these agencies constitute a sufficiently broad field of activity to warrant cabinet status for this agency. On the way out a session with Mary Switzer, who is the right hand of the administrator and who keeps her finger on the pulse of the agencies under his supervision.

—19th and 20th—

Grinding away at the post-convention chores and endeavoring to obtain a firm commitment from the construction company as to the date of completion of the war memorial. It looks as though the dedication ceremonies may have to be postponed until spring because of the uncertainties of the delivery of the bronze section of the memorial and consequent completion too late for an outdoor ceremony this fall.

Late in the evening to Trenton, N. J., and an early Saturday visit with Secretary Debus of the New Jersey Pharmaceutical Association and Secretary Powers of the State Board of Pharmacy.

—22nd—

A lengthy discussion with Capt. Eaton and Comdr. Lyons of the U. S. Navy who are working on the regulations for activating the Medical Service Corps, with many a new problem posed for the Navy which has never had commissioned pharmacists among the personnel of the regular Navy.

—23rd—

Much activity in completing the work of the day and preparing for the trip to Louisville to address the Kentucky Pharmaceutical Association. Off on the "National Limited" for Louisville at 5:30 p. m., enjoying a good dinner on the train and finding time to catch up with essential reading.

—24th—

A profitable day spent at Louisville, Ky., first with the Kentucky Pharmaceutical Association, addressing them in the morning on "New Horizons for Pharmacy in the United States," then visiting the Louisville College of Pharmacy where classes were just getting under way. Busy Kentucky Association Secretary Josey turned us over to Tom Hoskins who knows his way around among the prescription compounders and was able to show us

the cream of professional pharmacy in Louisville before train time.

At 5:50 on the "Diplomat" to Washington with a bevy of Republican women bound for a three-day sojourn in the nation's capital occupying a full car and making the diner a lively place. At our table was one good lady who had never eaten a meal on a railroad diner and had not traveled by rail for more than thirty years. It is good to see these folks getting a first-hand view of what goes on in Washington, albeit the impression may be similar to those of foreign visitors to the United States who spend a day here and there and then write a book with expert opinions on how the government works.

—25th—

Returning to Washington shortly after noon found many a telephone call to be returned. From Gen. Armstrong came the good news that Lt. Col. Othmar F. Goriup, a pharmacist, had been officially named to head the Medical Service Corps of the U. S. Army as the first chief of that new division of the Medical Department.

—26th—

Much grief connected with the installation of a new oil tank to feed the heating system at headquarters. One gets a taste of the unsatisfactory conditions surrounding the construction industry these days, with impossible promises carelessly carried out and everybody getting sour and disgusted with everybody else. But if the construction industry is in difficulties, what of the director of the Pharmaceutical Survey with whom we had lunch today at the Cosmos Club? If each of the various subdivisions of American pharmacy could prevail upon the good doctor to listen to its tale of woe alone and shape the recommendations without reference to other tales of woe, there would be at least ten divergent final reports—but the director is permitted to make only one final report.

—27th—

Greatly saddened by telephone information from Dean Serles of the untimely passing of Elmer Wirth, pharmacognosist of note and co-worker in the field of general pharmacy. Such men can ill be spared at a time when pharmacy is short of teaching personnel and scientific leadership.


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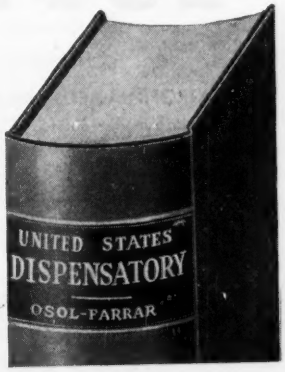


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## HEADQUARTERS (from page 535)

adequate labeling, it has been twisted into a law that promotes self-medication. Those who seek to increase the exemptions from the restrictive provisions of the pharmacy laws have taken advantage of the confusion with respect to warning regulations to proclaim that there exist today only two types of drugs, to wit: those to be sold as packaged medicines across the counter and those limited to prescription. Based on such a premise the Pharmacy Act which contains an exemption, such as "nothing in this Act shall be construed to apply to the sale of commonly used household remedies and other products packaged and labeled in accordance with the Food, Drug and Cosmetic Act," would serve to make a vast majority of all drugs and medicines salable without professional supervision.

Many of the men in the proprietary medicine industry today are pharmacists. Many have contributed to worth-while causes in pharmacy. Many have contributed to the support of colleges of pharmacy through the American Foundation for Pharmaceutical Education. It seems very difficult to believe that the legislative representatives of the Proprietary Association are carrying out the wishes of these men. One cannot conceive of the existence of individuals in this industry who would be so shortsighted as to support the development of colleges of pharmacy and the recruitment of students for these colleges only to turn them out as registered pharmacists limited in their responsibility to the compounding of prescriptions and the sale of such highly toxic drugs as require unusual safeguards, which even the representatives of the Proprietary Association admit are dangerous to the public.

We prefer to believe that some enthusiastic legislative representative or paid organizer has overstepped the mark in this matter and needs to be called to order by the Proprietary Association.

We regret the necessity for a public discussion of this matter even in a professional publication. However, it has reached the point where we should have a showdown and name the producers of pharmaceuticals who deliberately plan to bypass the pharmacy as the properly constituted legal outlet for drugs and medicines. Helping to create a new and continually increasing group of outlets whose interest in the public health is zero, and who enter into this unholy alliance for no other reason than to increase their volume of sales regardless of the welfare of the public, is not a creditable activity for anyone connected with American pharmacy, to say the least.

If the full light of publicity is ever shed upon

this situation we have no doubt that public opinion will force members of state legislatures to take the same view of this problem which has been taken by the profession of pharmacy and the allied health professions.

## FIRST USP SUPPLEMENT ISSUED

The first sheet supplement to U. S. P. XIII has been issued by the Committee of Revision. The supplement includes a number of changes that should be in the hands of every owner of a Pharmacopœia, Dr. E. Fullerton Cook, Committee chairman, points out.

Copies are available on request from the U. S. P. Revision Committee, 4738 Kingsessing Ave., Philadelphia 43.

## WILLIAM C. ANDERSON DIES; WAS HONORARY HEAD OF A. PH. A.

Dr. William C. Anderson, a former honorary president of the AMERICAN PHARMACEUTICAL ASSOCIATION and dean emeritus of the Brooklyn College of Pharmacy, died at his home in Keyport, N. J., on September 3. He was eighty-two years old.

Dr. Anderson graduated in 1891 with the first class from the Brooklyn College. After practicing retail pharmacy for a number of years he sold his pharmacy to devote full time to the College as an educator and administrator. He was dean from 1902 until 1937 when he retired.

Among other posts he had held the presidency of the New York State Board of Pharmacy.

# ARCHAMBAULT HEADS U.S.P.H.S. PHARMACY SERVICE

GEORGE F. ARCHAMBAULT, Massachusetts pharmacist and lawyer, has been named chief of the newly organized pharmacy service in the Hospital Division of the U. S. Public Health Service. Mr. Archambault will direct a program to unify and develop the pharmacy service provided in all of the Service's 24 marine hospitals and in many of the medical relief stations, and to coordinate these activities with services of other professional groups.

Mr. Archambault brings to his position a broad background as pharmacist, pharmaceutical educator and administrator. He is a graduate of both the Massachusetts College of Pharmacy and the Northeastern University School of Law. Since 1931 he has been a member of the faculty of the Massachusetts College of Pharmacy in the departments of pharmacy and business administration. During the war years he was loaned by the College to the U. S. Public Health Service to serve as chief pharmacist at the U. S. Marine Hospital in Boston and to develop pharmaceutical service in that institution. Later, in 1946, he was granted a year's leave of absence to serve as director of professional relations for the Liggett Drug Co. in the New England states. He has also served as instructor in the Massachusetts Department of Education extension program as a lecturer on drugstore management.

Mr. Archambault holds membership in the AMERICAN PHARMACEUTICAL ASSOCIATION, American Society of Hospital Pharmacists, the Boston and Cambridge Bar Associations and is a member of the Rho Chi honorary fraternity. His publications on pharmaceutical jurisprudence, management and professional relations have appeared in this and other journals.

GEORGE F. ARCHAMBAULT

# New A. Ph. A. Members

The American Pharmaceutical Association extends a cordial welcome to the men and women joining in its expanded program on behalf of the profession. Those accepted for active membership during the month preceding September 20 are listed below.

### NEW LIFE MEMBERS

**Rothrock, Russell B.,** Evansville, Ind.
**Christian, John E.,** W. Lafayette, Ind.
**Wilson, Stephen,** Pittsburgh, Pa.
**Netz, Charles V.,** Minneapolis, Minn.
**Merchant, Eugene E., Jr.,** Columbia, S. C.
**Data, John B.,** Lafayette, Ind.

### CALIFORNIA

Atchley, Homer E., Yreka
Dickenson, Alden, Yreka
Elmore, Paul Roy, Petaluma
Greene, Earl C., Yreka
Hickey, E. A., Weed
Jones, Cethil, Dunsmuir
Kimes, Gloria F., San Francisco
King, F. T., Dunsmuir
Prell, Morris, Long Beach
Teshima, Henry, San Francisco

### CONNECTICUT

Pelchar, John Arthur, Terryville

### DISTRICT OF COLUMBIA

Hocking, Harold J., Washington

### GEORGIA

Dunaway, W. H., Marietta

### IDAHO

Pirquet, Vera, Sun Valley

### ILLINOIS

Allison, Charles B., Chicago
Gronau, Arthur P., Chicago
Metzler, Kenneth R., Waukegan
Stanish, Edward S., Highland Park
Thoennes, Lawrence A., Chicago
Thompson, Robert Edward, Lisle
Wiertelak, Albert P., Chicago

### INDIANA

Perrin, R. C., Muncie

### MAINE

Frawley, Francis A., Bangor

### MICHIGAN

Bailey, Louis, Detroit
Bodt, George W., Detroit
Hamaker, Ambrose C., Dearborn
Shepard, Samuel, Detroit
Stein, Louis S., Hibbing

### MINNESOTA

Dahl, Joseph E., Minneapolis
Pasternacki, John G., Virginia

### MISSOURI

Grosicki, Thaddeus Stanley, St. Louis
Weaver, Jesse H., Overland

### MONTANA

Durham, William H., Missoula

### NEW HAMPSHIRE

Abbott, John H., Concord

### NEW JERSEY

Barney, L. D., Nutley
Charnowitz, Charles H., Bloomfield
Howland, Frank O., Jr., Glen Rock

### NEW YORK

Firemark, Samuel, Laurelton
Frankel, Israel, Brooklyn
Sister Mary Columba, Harrison
Steinmann, Herbert R., New York
Stern, Lewis W., New York
Turner, Richard T., New York
Woodward, Edson F., Mt. Vernon

### OHIO

Freking, Harold C., Cincinnati
Sister Mary Paul Johnston, Cleveland

### OREGON

Knight, R. Lee, Portland
Sather, Victor A., Silverton

### PENNSYLVANIA

Benson, Alfred J., Scottdale
Dozois, K. Pierre, Ambler
Frye, Lamar F., Philadelphia
Moll, Russell O., Reading

### RHODE ISLAND

Navach, Joseph F., Warren

### TEXAS

Connor, Charles M., El Paso

### UTAH

Neeley, A. LeRoy, Salt Lake City
Sundberg, Jack C., Salt Lake City

### WISCONSIN

Aune, Roy A., Ladysmith
Bahringer, Wallace H., Milwaukee
Barrows, Hollis T., Milwaukee
Bookstaff, Samuel B., Milwaukee
Burg, Chester J., Elkhorn
Coyne, John L., Milwaukee
Duffner, Roy A., Milwaukee
Gehrs, Kathryn D., Milwaukee
Haberle, Martin F., Milwaukee
Harris, Gordon, Milwaukee
Iverson, Arthur M., Cambridge
Kyes, Leslie H., Milwaukee
Leverenz, Charles E., Milwaukee
Maloney, F. J., Wauwatosa
Mathes, E. H., Milwaukee
McAllister, Francis A., Sr., Milwaukee
Moen, Reuben E., Milwaukee
Mooney, Wm. P., West Allis
Mueller, Carl F., Milwaukee
Muth, John H. Milwaukee
Nelson, Sherwood E., Milwaukee
Porter, William R., Racine
Rubin, Harry C., Milwaukee
Schulkin, Joseph, Madison
Schulz, Donald Walter, Darlington
Sister M. Blanche Noe, Milwaukee
Stark, Ralph H., Milwaukee
Steffens, Ralph J., Milwaukee
Tanty, Emil G., Milwaukee
Weinkauf, Fred W., Milwaukee
Winiarski, Mrs. Gertrude, Milwaukee

### FOREIGN

Candal, Joaquin Lopez, Fajardo, Puerto Rico
Dean, Royal George, Hawaii
De Leon, J. Alfonso, Mexico City, Mexico
Fahmy, Ibrahim Ragab, Cairo, Egypt
Northgraves, Orlean M., Toronto, Ontario, Can.
Peterson, Mervin Roland, Saskatoon, Can.

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